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VOLUME 83 NUMBER 5

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

November, 1948

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PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

Made in United States of America

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BULLETIN
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This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Post Office. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

THE CULTURAL DIFFERENTIATION OF PARACOLON BACILLI

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Received for Publication April 26, 1948

The identification of paracolon bacilli and the differentiation of these organisms from *Salmonella*, *Shigella*, *Proteus*, and other Gram negative bacilli which fail to ferment lactose, present one of the most difficult problems in diagnostic bacteriology. This problem was emphasized and discussed in a previous report on the relation of paracolon bacilli to urinary tract infections (Schaub, 1946). The investigation to be reported here was undertaken with the hope of finding a method for the differentiation of paracolon bacilli from culturally similar *Enterobacteriaceae* and for the classification of the paracolon bacilli.

Cultural studies of paracolon bacilli by Stuart, Wheeler, Rustigian, and Zimmerman (1943) resulted in the now generally accepted practice of differentiating these Gram negative bacilli into paracolon *Escherichia*, paracolon *Aerobacter* and paracolon intermediate on the basis of their IMViC* formulae. This method of differentiation parallels the classification by Parr (1936) and Stuart, Griffin and Baker (1938), of the typical coliform bacilli into *Escherichia*, *Aerobacter* and intermediates on the same basis; that is, by their indol, methyl red and Voges-Proskauer reactions and utilization of citrate as the sole source of carbon. Borman, Stuart and Wheeler (1944) suggested the generic name *Paracolobactrum* for the paracolon bacilli and the division of this genus into *Paracolobactrum aerogenoides*, *Paracolobactrum intermedium* and *Paracolobactrum coliforme* on the basis of acetyl methyl carbinol production and utilization of citric acid as sole carbon source. Michael and Harris (1945) also concluded, as the result of a cultural study of a group of paracolon bacilli, that, other than the IMViC reactions, no biochemical properties could be considered characteristic of any one

*IMViC is a mnemonic formula proposed by Parr (1938) and expresses the results of the indol, methyl red and Voges-Proskauer reactions and the utilization of citrate as the sole carbon source.

group of paracolon bacilli and that there was no cultural basis for classification except by determination of IMViC formula. Certain types or sub-groups of paracolon bacilli have been the subject of special biochemical and serological investigation (Peluffo, Edwards and Bruner, 1942; Edwards, Cherry and Bruner, 1943; Edwards, 1945; Hinshaw and McNeil, 1945; Barnes and Cherry, 1946; Stuart and Rustigian, 1943, Stuart, Wheeler and McGann, 1946; Galton, Hess and Collins, 1947). However, these types have been selected primarily on the basis of their probable pathogenicity for man and animals, and these reports have not contributed to the differentiation of the paracolon group as a whole.

In our laboratory fifty-six strains of paracolon bacilli, with but one exception from human sources, have been studied. Sixteen of these cultures were received from Dr. L. W. Parr of George Washington University, twelve from Dr. C. A. Perry and A. A. Hajna of the Maryland State Department of Health, four strains from Dr. R. V. Stone of the Los Angeles Health Department and one from Mr. T. C. Buck, Baltimore City Health Department. The remaining twenty-three strains were recently isolated in laboratories of the Johns Hopkins Hospital from a variety of clinical material, for the most part urine and stool cultures. One hundred control cultures, consisting of a number of strains each of *Escherichia*, *Aerobacter*, intermediate coliform bacilli, *Salmonella*, *Shigella*, *Eberthella*, *Proteus*, *Pseudomonas*, *Serratia*, *Alkaligenes*, *Vibro* and a few miscellaneous Gram negative bacilli were also included in the series.

The usual biochemical tests used in the differentiation of Gram negative bacilli were employed in the preliminary study of these cultures. These were: 1) the fermentation of lactose, dextrose, sucrose, xylose and mannitol, 2) the production of indol, the methyl red and Voges-Proskauer reactions and the utilization of citrate; that is, determination of IMViC formula, and 3) reduction of nitrates, production of hydrogen sulfide, utilization of sodium malonate (Leifson, 1933) and liquefaction of gelatin. This cultural study yielded the anticipated results, that the paracolon bacilli could be classified as paracolon *Escherichia*, paracolon *Aerobacter*, and paracolon intermediate on the basis of their IMViC formula, and that these biochemical reactions would not allow rapid differentiation of the paracolon bacilli from *Salmonella*, *Shigella*, *Proteus*, and other non-coliform organisms.

A number of special media recently suggested for the differentiation of paracolon bacilli from *Salmonella*, *Shigella* and *Proteus* were then studied. These included the multiple sugar medium and 10% lactose agar slants of Chilton and Fulton (1946) and Christensen's urea agar (1946). In the multiple sugar medium, which contains adonitol, aesculin, salicin and sucrose and in which fermentation indicates paracolon bacilli as differentiated from *Salmonella*, which fail to ferment any of these carbohydrates, our results closely approach those of Chilton and Fulton, 33% of the paracolon bacilli in our series giving a positive reaction. However, the low percentage of paracolons which give fermentation in this medium does not recommend it for the differentiation of paracolon bacilli from the non-coliform Gram negative bacilli which give a negative reaction. The agar slants containing 10% lactose were also found to be of little value, since only 21% of our paracolon bacilli showed fermentation in 24 hours on this medium, while 20 strains of supposedly lactose-negative Gram negative bacilli in the control series, including strains of *Eberthella*, *Shigella* and *Salmonella*, gave an acid reaction.

Christensen's urea agar indicated urease production by 29% of the paracolon bacilli studied, thus differentiating these strains from the urease-negative *Salmonella*, *Shigella* and *Eberthella*. The delayed reaction of the paracolon bacilli as contrasted with the rapid urease production by *Proteus* was useful in differentiating these organisms, as pointed out by Christensen. However, the small percentage of paracolon bacilli found to produce urease detracts greatly from the value of the urea agar for the differentiation of paracolon bacilli from other *Enterobacteriaceae*.

Therefore, since neither the usual methods for the biochemical differentiation of Gram negative bacilli nor the new media suggested by Chilton and Fulton and by Christensen seemed to solve the problem of identifying paracolon bacilli or rapidly differentiating them from *Salmonella* or *Shigella* and other non-coliform Gram negative bacilli, the following investigation was undertaken.

It is well known that the growth of the typical coliform bacilli, *Escherichia*, *Aerobacter*, and the intermediate group, is inhibited on certain media designed for the isolation of the intestinal pathogens and for the inhibition of the normal intestinal Gram negative bacilli. It seemed possible that the paracolon bacilli also might be selectively

inhibited on such media, since they are generally regarded as atypical or aberrant forms of normal coliform organisms. Therefore, the growth of the paracolon bacilli in our series, as well as that of all of the control cultures, was studied on such media. (Schaub, 1947)

Inhibition of growth on Baltimore Biological Laboratory desoxycholate-citrate and desoxycholate-citrate-lactose-sucrose agar and on Difco-Salmonella-Shigella (S.S.) agar was first determined. In preliminary trials, S.S. agar was found to give the best results, inhibition of growth on desoxycholate-citrate-lactose-sucrose agar being almost as satisfactory. S.S. agar was therefore selected as the test medium for the original study. However, we were unable to obtain information as to the composition of Difco bile salts no. 3, which is one of the active ingredients of S.S. agar, and since, therefore, the formula of S.S. agar is not completely known, and since it is over complicated for our purpose, the development of a suitable medium of known composition was undertaken. This investigation has led to the development of a simple coliform inhibiting medium with the following formula:

Beef extract	0.5%
Sodium citrate	1%
Sodium desoxycholate	0.25%
Sodium thiosulfate	1%
Trypticase	0.5%
Agar	1.4%

pH 7.1

This coliform inhibiting medium, which will be referred to hereafter in this report as C.I. agar, has been found to give the same results as were obtained with Difco S.S. agar, that is, excellent inhibition of the typical coliform bacilli and closely related paracolons, while supporting the growth of the control cultures and of certain paracolon bacilli, as will be described.

In this investigation, C.I. and S.S. agar have been used both as agar plates and slants with equally good results. S.S. agar was prepared from the dehydrated, commercial product as directed, without sterilization, and distributed asceptically into sterile petri dishes or into sterile test tubes and slanted. C.I. agar was prepared according to the formula given above with a minimum of heating and also distributed asceptically into sterile petri dishes or into sterile test tubes and slanted.

In the asceptic tubing of both these media only simple precautions need be taken since the media will not support the growth of common contaminants.

In testing simultaneously a large number of cultures, both C.I. and S.S. agar have been used in petri dishes. A plate may be divided into as many as twelve segments and each segment streaked lightly with a proper dilution of the culture as will be described. In testing single cultures, the media tubed and slanted is preferred, since a relatively small surface area gives better evidence of the presence or absence of inhibition than if an entire plate is inoculated with a diluted culture. In using S.S. agar, the medium in slants was found to have the added advantage of demonstrating hydrogen sulfide production as satisfactorily as the lead acetate medium used for this purpose, the medium at the base of the slant becoming markedly blackened when the surface of the slant is streaked with a hydrogen sulfide producing organism. C.I. agar gives only slight evidence of hydrogen sulfide, and this irregularly and only after 48–72 hours incubation.

On both the C.I. and S.S. agar, inoculation with undiluted broth cultures was found to give unreliable results. However, if diluted cultures are used, consistently satisfactory, reproducible inhibition of the typical and aberrant coliform bacilli was obtained. The dilution factor operates within very broad limits, it having been demonstrated that a dilution of one loopful of a 24-hour broth culture in broth or saline in amounts varying from 2 to 15 cc gives equally good results. In this study we have consistently used a well shaken dilution of a loopful of a 24-hour broth culture in 10 cc of sterile isotonic salt solution. It has also been demonstrated that comparable results can be obtained by fishing directly from a colony on desoxycholate agar to 10 cc of sterile salt solution, using the saline suspension for the inoculation of the test medium.

Using the techniques described above, inhibition of the coliform and closely related paracolon bacilli is usually complete. Occasionally one or two colonies of these organisms are found on either of the coliform inhibiting media. Inhibition of growth, however, is definitely indicated in such instances, as the cultures in which no inhibition occurs give numerous colonies when a diluted inoculum is used. It should be emphasized that results must be read after 18–24 hours incu-

bation. After longer periods of incubation growth may occur in cultures which were completely inhibited in 24 hours.

Studying the growth of diluted and undiluted cultures on both C.I. and S.S. agar as described, it was found that the growth of the typical coliform bacilli, *Escherichia*, *Aerobacter* and the intermediates, was inhibited, while a majority of the control cultures, including *Salmonella*, most *Shigella*, *Eberthella*, *Proteus* and *Pseudomonas*, grew well. The notable exceptions in the control series were several old stock strains of *Shigella dysentesriae*, which were inhibited irregularly on both media, and all three strains of Proteus morgani, which were completely inhibited on C.I. agar while growing well from a diluted inoculum on S.S. agar. Also inhibited on both C.I. and S.S. agar were all strains of *Serratia marcescens*, *Alkaligenes faecalis*, *Bacterium bronchisepticum* and *Vibrio comma*, *Vibrio metchnikovi* and *Vibrio proteus*. However, since these latter organisms may be readily differentiated from paracolon bacilli, their failure to grow on C.I. and S.S. agar is not considered to detract from the value of these media as used for the identification of paracolon bacilli.

When the paracolon bacilli in our collection were studied on these media, it was found that the growth of a large number was inhibited, while others grew equally as well as the control cultures. When the fact of growth or inhibition on coliform inhibiting media was correlated with the results of the cultural study, all of the paracolon bacilli in our series were found to fall into one of four groups, which for the sake of convenience have been designated Groups I, II, III, and IV. (Table I).

The paracolon bacilli whose growth was inhibited on C.I. and S.S. agar are included in Group I. In this respect, that is, inhibition on the test media, and in other cultural characteristics as well, these paracolon bacilli resemble the coliform bacilli, differing from the typical coliforms only in their failure to ferment lactose promptly with acid and gas. Stuart, Mickle and Borman (1940) have suggested the term "aberrant coliform" for the slow-lactose-fermenting coliform organisms, and this term may well be applied to these Group I paracolon bacilli. Stuart and his associates (ibid) suggested that the aberrant coliforms be

TABLE I

Cultural Differentiation of Paracolon Bacilli

ORGANISM	MOTILITY	LACTOSE	DEXTROSE	SUCROSE	XYLOSE	MANNITOL	INDOL	METHYL RED	VOGES-PROSKAUER	CITRATE	MALONATE	NITRATES	HYDROGEN SULFIDE	UREASE	GROWTH OF DILUTED CULTURE ON C.I. OR S.S. AGAR
Group I paracolon bacilli															
Paracolon *Escherichia*	+/−	late Ag, A only or negative	Ag/A	Ag/A/−	Ag/A	Ag/A	+	+	−	−	−	+	−	−	−
Paracolon *Aerobacter*	+/−	late Ag, A only or negative	Ag/A	Ag/A	Ag/A	Ag/A	−	−	+	+	+	+	−	+/−[3]	−
Paracolon intermediate	+/−	late Ag, A only or negative	Ag/A	Ag/A/−	Ag/A	Ag/A	Combination other than those above				+/−	+	−	+/−	−
Group II paracolon bacilli[1]	+	late Ag	Ag	−/Ag	Ag	Ag	−	+	−	+	−/+	+	+	+/−	+
Group III paracolon bacilli	+	Negative	A[2]	A late	−	−	+	+	−	+	−	+	+w	−	+
Group IV paracolon bacilli	+	late A or negative	A, sl. gas	−/A, sl. gas	Ag/A	Ag/A	−	+	+	+w	+	+	−	−	+

Ag = acid and gas; A = acid only; sl. = slight; w = weak; +/− = some strain positive, some negative.

[1] For differentiation of the subgroups of Group II paracolon bacilli, see Table III

[2] Some strains produce a bubble of gas in dextrose Durham tubes.

[3] + = slight urease production in 24 hours, increasing on further incubation, on Christensen's urea agar.

classified by their reaction in lactose Durham tubes and described the following groups:

a) late-lactose-fermenting, micro-aerogenic, which fail to produce acid and 20% or more gas in lactose broth in 48 hours.
b) anaerogenic, which ferment lactose in 24 hours or longer with the production of acid but no gas.
c) papillae-forming strains, which ferment lactose slowly with acid and gas and which, on desoxycholate or eosin-methylene-blue agar, produce colored secondary colonies, transplants from which ferment lactose in 24 hours. These include the organisms generally known as Escherichia coli-mutabile (Neisser, 1906, Massine, 1907, Parr, 1939) but the group is not limited to paracolon *Escherichia*.
d) strains which fail completely to ferment lactose.

The paracolon bacilli of Group I of our series may be classified by their fermentation of lactose in this manner, and examples of each fermentative type have been found in the cultures studied. It is interesting to note that with but one exception, all the strains of paracolon *Escherichia* which fermented lactose slowly produced papillae-forming colonies on desoxycholate agar, either readily on first isolation or after a number of subcultures. Only one strain each of paracolon *Aerobacter* and paracolon intermediate were found to produce such secondary colonies.

As has been previously mentioned, Stuart, Wheeler, Rustigian and Zimmerman (1943) and Borman, Stuart and Wheeler (1944) introduced the classification of paracolon bacilli as paracolon *Escherichia*, paracolon *Aerobacter* and paracolon intermediate by IMViC formula. As shown in Table II, the Group I paracolon bacilli, those whose growth is inhibited on C.I. and S.S. agar, may be thus differentiated by their indol, methyl red, Voges-Proskauer and citrate reactions. As far as other biochemical reactions are concerned, there is no correlation between the results in Chilton and Fulton's multiple sugar (Aass) medium and differentiation by IMViC formula, while on Christensen's urea agar paracolon *Escherichia* were uniformily negative and paracolon *Aerobacter* and paracolon intermediates were found to be less than 50% positive. Other cultural characteristics are shown in Table I.

The strains of paracolon bacilli comprising Group I were isolated

from both normal and pathologic stool specimens, from urine, from blood and body fluid cultures taken at autopsy, and from ear cultures. The percentage occurrence of this and the other groups of paracolon bacilli in our series is not significant, since they do not represent a continuous series, and the strains received from Dr. Parr, Dr. Perry and Mr. Hajna, and Dr. Stone represent selected strains from their collections. However, since efforts to obtain additional freshly isolated strains of Group II, III and IV paracolons have been unsuccessful, and since Group I cultures are encountered with great frequency in the routine laboratories of the Johns Hopkins Hospital, it is evident that the aberrant coliform bacilli of Group I are by far the most common paracolon bacilli encountered in clinical material from human sources. Using inhibition on C.I. or S.S. agar as a screen test, these organisms may be rapidly differentiated from non-coliform bacilli, such as *Salmonella*, *Shigella* and *Proteus*, which they may resemble culturally.

Thirty seven of the paracolon organisms in our series failed to grow on C.I. or S.S. agar, and are so included in Group I just described. The remaining nineteen strains grew well under the test conditions. If classification by IMViC formula alone was applied, without reference to growth on the test media, then these organisms would be indiscriminately classified as paracolon intermediates. But if they are separated from the aberrant coliform bacilli of Group I by the fact of their growth on coliform inhibiting media, then these organisms fall into three well defined groups, Group II, Group III and Group IV.

The outstanding common characteristic of Group II paracolon bacilli, as shown in Table I, is their production of hydrogen sulfide. They are all motile Gram negative bacilli which ferment lactose slowly, in from 2–10 days, with the production of acid and slight gas, serial transfer in lactose broth resulting in fermentation in 24 hours. Dextrose and mannitol are fermented promptly with acid and gas. An IMViC formula of $- + - +$ is common to the group.

Other biochemical characteristics of the Group II paracolon bacilli in our collection have shown these organisms to fall into three well defined cultural sub-groups, as shown in Table II. The organisms of sub-group A are characterized by the production of urease as demonstrated on Christensen's urea agar, though the reaction is weak and delayed as compared with that of *Proteus*. They also may be readily

recognized by the presence of a marked and distinctive odor resembling that of spoiled cabbage. These strains correspond to the description published by Barnes and Cherry (1946) of a group of paracolon bacilli isolated from a small outbreak of gastroenteritis in Bethesda, Maryland. Dr. P. R. Edwards has kindly studied the strains comprising Group II-A, and has classified them (Edwards, 1947) as belonging to what he refers to as the "Bethesda Group", which group includes the strains from gastroenteritis described by Barnes and Cherry. The strains of sub-group A in our series were also isolated from stool specimens from patients with gastroenteritis.

Sub-group B of Group II paracolon bacilli differs from sub-Group A in fermenting sucrose and in producing acid and gas in Chilton and Fulton's multiple sugar medium, probably due to fermentation of the sucrose in this medium. These organisms also possess the distinctive characteristic of growing on nutrient agar containing 1/5000 potassium tellurite. The only other Gram negative bacilli found to grow on tellurite agar of this concentration are *Proteus mirabalis*, *P. vulgaris*, *P. morgani* and *Pseudomonas aeruginosa*. It is possible that the sucrose-positive, hydrogen-sulfide-positive, urease-producing paracolon bacilli reported by Christensen (1947) may be of this group.

Sub-group C of Group II paracolon bacilli may be differentiated from Group II-A and Group II-B by failure to produce urease, by utilization of sodium malonate, by lack of the distinctive cabbage odor and by slow liquefaction of gelatin. Culturally these organisms correspond to descriptions published by Peluffo, Edwards and Bruner (1942), Edwards, Cherry and Bruner (1943) and Hinshaw and McNeil (1945) of paracolon bacilli isolated from warm and cold blooded animals and turkeys, which organisms are serologically related to the genus *Salmonella*. In only one instance, Edwards (1945), has a paracolon bacillus of this group been reported from a human infection. The one strain of Group II-C in our collection was received indirectly from Dr. Hinshaw and was isolated from a rattlesnake.

These hydrogen sulfide producing paracolon bacilli of Group II may, on superficial cultural examination, be confused with *Salmonella* or *Proteus*, but they may be readily differentiated culturally as shown in Table II. *Proteus* may be eliminated by the use of either Rustigian and Stuart's (1941) or Christensen's (1946) urea media. Sub-groups

A and B may be rapidly differentiated from *Salmonella* by urease production on Christensen's urea agar, less specifically by the distinctive cabbage odor, and eventually by their late fermentation of lactose. Sub-group C can be differentiated from *Salmonella* by utilization of sodium malonate and by the slow lactose fermentation and delayed gelatin liquefaction of these paracolon bacilli.

Group III includes a well defined group of anaerogenic paracolon bacilli which grow well on S.S. and C.I. agar. As shown in Table I, they fail to ferment lactose, xylose and mannitol while fermenting dextrose with the production of acid and usually no gas, although occasionally a small bubble of gas may be formed. Sucrose is fermented slowly, in from 4–6 days, with acid only. Indol is produced and citrate utilized (IMViC + + − +), while the reaction on Christensen's urea agar is negative. In lead acetate medium, hydrogen sulfide is produced, but the reaction is weak.

These Group III paracolon bacilli, the four strains of which in our collection were isolated from patients with intestinal infections, are culturally identical with paracolon bacilli Type 29911 as described by Stuart, Wheeler and McGann (1946). Stuart and his associates concluded, after an extensive study of their Type 29911 cultures, that they appear to be an intermediate group between *Proteus* and *Shigella*, a concept borne out by our results. Culturally, Group III paracolon bacilli closely resemble *Proteus rettgeri*, but they may be easily differentiated by the strong urease production of the later.

The biochemical characteristics of Group IV paracolon bacilli are shown in Table I. Like Groups II and III, their growth is not inhibited on either of the coliform inhibiting media, so that they may be readily differentiated from the commonly occurring Group I organisms. The outstanding cultural characteristic of Group IV paracolon bacilli is their utilization of sodium malonate as the sole source of carbon. The ability to utilize sodium malonate or malonic acid is a valuable differential characteristic, since it is shared by a relatively few Gram negative bacilli, namely *Aerobacter* and Group I paracolon *Aerobacter*, some strains of intermediate coliform bacilli and Group I paracolon intermediates, Group II-C and Group IV paracolon bacilli and also *Pseudomonas aeruginosa*. Of these malonate-positive organisms, only *Pseudomonas* and Group II-C and Group IV paracolon bacilli will grow

on coliform inhibiting media, and the malonate-positive paracolons may be readily differentiated as shown in Tables I and II.

TABLE II

Differentiation of Group II Paracolon Bacilli

ORGANISMS	HYDROGEN SULFIDE	LACTOSE	SUCROSE	UREASE[1]	GELATIN	MALONATE	CABBAGE ODOR	GROWTH ON AGAR CONTAINING 1/5000 POTASSIUM TELLURITE
Group II—A paracolon bacilli	+	late AG	−	+	−	−	+	−
Group II—B paracolon bacilli	+	late AG	AG	+	−	−	+	+
Group II—C paracolon bacilli	+	late AG	−	−	+ slow	+	−	−
Salmonella	+/−	−	−	−	−	−	−	−
Proteus vulgaris mirabalis	+	−	AG 1–7 days	++	+	−	−	+
Proteus morgani	+	−	−	++	−	−	−	+
Proteus rettgeri	−	−	−	++	−	−	−	−

AG = acid and gas;

[1] + = slight urease production in 24 hours, increasing on further incubation

++ = slight urease production in 6 hours or less, reaction complete in 24 hours

Urease production demonstrated on Christensen's urea agar.

Other biochemical reactions of Group IV paracolon bacilli are shown in Table I. These organisms have an IMViC formula of − + + +, and weak and delayed utilization of sodium citrate is characteristic of the group. Lactose is fermented slowly (2–3 weeks) by two strains, while no definite fermentation by the other four strains was observed after two months incubation. Other carbohydrates are fermented in 24 hours. These organisms are weakly aerogenic, some strains being completely anaerogenic on first isolation but producing small amounts

of gas in subcultures. In all cases dextrose is fermented with acid and gas, but the production of gas in the fermentation of other carbohydrates is irregular and inconsistent. Gas formation in lactose Durham tubes has not been observed, while in the fermentation of sucrose, xylose and mannitol gas may or may not be produced.

No description of the organisms included in Group IV could be found in the literature. Although the number of strains is too small to be significant in respect to probable pathogenicity, it should be noted that all were isolated from patients with diarrhea and that efforts to find similar organisms in other clinical material have been unsuccessful to date.

DISCUSSION

The differentiation of paracolon bacilli here suggested presents nothing radically new or different, but follows the pattern already established by the reports of other investigators. It follows the suggestion of Stuart and his associates (Stuart, Mickle and Borman, 1940; Stuart and Rustigian, 1943; Stuart, Wheeler and McGann, 1946) that the paracolon group includes the aberrant coliform bacilli and also other Gram negative bacilli which appear to be intermediate between the coliform group and various non-coliform genera such as *Salmonella*, *Proteus* and *Shigella*. Under the system of differentiation just described, the Group I paracolon bacilli, which behave as do the coliform bacilli on C.I. and S.S. agar, appear to be aberrant coliforms, while Groups II, III and IV appear to be intermediate forms between coliform and non-coliform organisms.

In our laboratory the determination of growth or inhibition on either the coliform-inhibiting (C.I.) medium described, or on Difco S.S. agar, has served as a useful screen test in separating the aberrant coliforms of Group I from the other paracolon bacilli. However, the value of the test, in our opinion, lies not so much in its use in classifying the paracolon bacilli as in differentiating between the aberrant coliform bacilli of Group I and *Salmonella*, *Shigella*, and *Proteus*. Since the paracolon bacilli commonly encountered in various types of clinical material, particularly urine cultures and normal stool specimens, are of Group I whose growth is inhibited on coliform inhibiting media, this test has proved a valuable aid in the rapid identification of paracolon bacilli from human sources.

In the course of the investigation leading to the development of the new coliform-inhibiting medium, all the Gram negative bacilli in our collection were repeatedly tested over a period of ten months. During this time no alteration was noted in the inhibition of the typical coliforms or the Group I paracolon bacilli, or in the growth of stock cultures of Groups II, III and IV paracolon bacilli and the control cultures on C.I. or S.S. agar. However, preliminary studies of variants of paracolon bacilli have shown that rough and small colony variants of Groups II and IV paracolon bacilli fail to grow on C.I. and S.S. agar, while the smooth forms of these organisms consistently give good growth on these media. Stuart, Wheeler and McGann (1946) have reported similar inhibition in colonial variants of Type 29911 strains (Group III). With these exceptions, the characteristic of growth or inhibition on coliform inhibiting media appears to be a stable characteristic, and one that can be depended upon for the identification of newly isolated strains of paracolon bacilli.

The number of strains of paracolon bacilli included in our series is too few to draw any definite conclusions as to the relative pathogenicity of the four groups here described. However, in view of the fact that evidence for the etiological role of some strains of paracolon bacilli in gastro-enteritis is accumulating in the literature (Barnes and Cherry, 1946; Stuart and Rustigian, 1943; Stuart, Wheeler and McGann, 1946; Galton, Hess and Collins, 1947; Christensen, 1947), the source of our strains is interesting and possibly significant. Fifteen strains of paracolon bacilli received from Dr. Parr were isolated from normal feces, and all were inhibited on S.S. and C.I. agar and so classified as Group I. The remaining twenty-two strains of Group I paracolon bacilli were isolated from a variety of clinical material, primarily urine cultures, stool specimens and autopsy material. Their occurrence is, therefore, the same as that of the typical coliforms and such as would be expected of aberrant coliform bacilli. The sixteen strains comprising Group II-A, Group III and Group IV were all isolated from patients with diarrhea or gastro-enteritis. No strains of these groups have been isolated from normal stool specimens or from other clinical material. Since Groups II, III and IV paracolon bacilli are not inhibited on S.S. agar or C.I. agar and are, therefore, differentiated from the typical and aberrant coliform bacilli of the normal intestinal tract, and since these organisms appear to be intermediate forms between

coliform bacilli and *Salmonella*, *Proteus* and *Shigella*, their etiological significance in intestinal disease as suggested by their occurrence in pathologic stool specimens does not seem improbable.

SUMMARY

1. On a simplified desoxycholate-citrate-thiosulfate medium (coliform-inhibiting or C.I. agar) and on Difco S.S. agar, the growth of typical coliform bacilli is inhibited. On either of these media, using a properly diluted culture as an inoculum, the growth of a large number of paracolon bacilli is also inhibited.

2. Correlating growth or inhibition on C.I. or S.S. agar with biochemical characteristics, the paracolon bacilli in our series fall into four large groups and a number of sub-groups:

Group I—aberrant coliform bacilli, consisting of paracolon *Escherichia*, paracolon *Aerobacter* and paracolon intermediates; growth inhibited on coliform inhibiting media.

Group II—hydrogen-sulfide-producing paracolon bacilli; growth not inhibited on coliform inhibiting media. This group may be divided culturally into three sub-groups, II-A, II-B and II-C.

Group III—anaerogenic paracolon bacilli; growth not inhibited on coliform inhibiting media (Stuart Type 29911).

Group IV—malonate-positive paracolon bacilli; growth not inhibited on coliform inhibiting media.

3. The use of C.I. and/or S.S. agar to determine growth or inhibition of an organism suspected of being a paracolon bacillus is recommended, not only for the possible classification of paracolon bacilli but also for the differentiation of the more commonly occurring Group I organisms from *Salmonella*, *Shigella*, *Pseudomonas* and *Proteus*.

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IRRADIATION OF LYMPHOID TISSUE IN DISEASES OF THE UPPER RESPIRATORY TRACT

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Received for Publication May 11, 1948

PHYSIOLOGICAL FUNCTIONS OF THE UPPER RESPIRATORY TRACT

The chief function of the upper respiratory tract is the modification of aspirated environmental factors. As in all complex mechanisms any one of a number of small defects may cause more or less serious limitations of function. From the medical point of view our chief interest is in the maintenance of normal function and the recognition and correction of minor defects before major difficulties arise.

Ordinarily, the air about us is below body temperature. It is always lower in humidity than the air in our lungs which is saturated with moisture. Frequently it contains a large quantity of dust and occasionally large foreign particles. Almost any bacterium or virus may be air borne and commonly travels on particles of dust. In ordinary respiration, 500 cc. of air passes through the nose on its way to the lungs in about two seconds. During this rapid passage gross particles of dust are removed at the nostrils and smaller particles become imbedded in the nasal mucus (1). The larynx is an additional protection against the passage of large foreign particles into the lungs. The inspired air is warmed to approximately body temperature and its water content greatly increased by its passage over the nasal, pharyngeal and tracheal mucous membrane (2).

Division of the nasal passages into two major parts by the septum and numerous smaller passages by the turbinates serves to provide a remarkably large mucous membrane area within the nose. In the normal nose the passage for air is at no point much wider than four or five millimeters; if both the turbinates and septum were removed, the inside of the nose would consist of a single cavity about 20 millimeters in width. This wide surface area provides a highly efficient humidifying and thermal control apparatus and an excellent opportunity for the removal of foreign material. The several smaller air streams into

which the main column of air is divided allows its passage with less turbulence.

The nasal mucous membrane, except at the vestibule and in the olfactory area, is composed of ciliated columnar epithelium. It is highly vascular and rich in mucous glands. Its thickness and vascularity can alter markedly with normal environmental fluctuations and with changes due to disease. The most important characteristics of this mucous membrane are: its large content of glands which provide a continual production of thin, tenacious mucus, and its ciliated epithelium (3). The ciliary movements throughout the nose are continually towards the nasopharynx (4–6). It has been calculated that ciliary action in the mucous membrane of the frog is so strong that in one minute one ciliated cell does work sufficient to lift its own weight 4.25 meters. This ciliary activity is extremely persistent in the face of widely varying conditions. A drop in temperature to 5° centigrade suspends ciliary activity only temporarily. Drying and excessive heat will incapacitate the cilia for a longer period. Ciliary activity remains normal as long as the nasal pH remains within the range 5.5 to 6.5 and it will often persist over a much wider range of pH change. During nasal disease, the pH of the nose becomes more alkaline; rest and sleep tend to restore the pH closer to the normal acidity. Ciliary movement within the sinuses moves any foreign material or mucus towards and through the sinus orifices where it joins the stream of mucus that is continually moving towards and into the nasopharynx. According to Hilding (4), mucus moves at a rate of four to six millimeters a minute, and small particles of foreign material have been observed to travel from the anterior end of the middle turbinate to the region of the eustachian tube orifice in four to ten minutes.

One of the commonest potential sources of ciliary trauma is nasal medication. Improper nasal medication may completely cripple the defenses of the nose in a matter of minutes. The use of an oily preparation overburdens and clogs ciliary action and at times causes complete cessation of ciliary motion. Two per cent sodium chloride solution or plain tap water is harmful to the nasal mucous membrane. Solutions of sodium salts of sulfonamides may permanently impair the function of cilia. Silver salt preparations may produce severe caustic

reactions on the mucous membrane and in addition may result in the deposit of silver in the skin, argyria (7–9).

There are several drugs which are harmless when administered in normal saline. Among these are neo-synephrine, ephedrine and penicillin. These drugs are most useful for nasal medication in the following concentrations—neo-synephrine $\frac{1}{4}\%$, ephedrine 1%, penicillin 1000 units per cc. Although the benzedrine inhaler has disadvantages in being a central nervous system stimulant and in having a very short action, it is harmless to the nasal mucous membrane and useful in some instances. There are, of course, other drugs that are beneficial in selected cases, but many of the nose drops in wide use are both harmful and useless. In any nasal medication the first question should be its possible toxic effects on the cilia and the mucous membrane of the nose.

Although a large surface area of mucous membrane and small airways are essential for optimum physiological function, these factors are peculiarly susceptible to serious interference from minor changes. Diffuse moderate inflammation or thickening of the mucous membrane, or minor anatomical abnormalities, may obstruct the passage of air through the nose or block the orifices of the paranasal sinuses. A septal deviation of two millimeters strategically located may upset the normal functioning of the nose. Diffuse thickening of the mucous membrane either from mechanical irritation, allergy, or infection may produce the same undesirable result. Abnormally functioning nasal passages may cause trouble in one of three ways: interference with the sense of smell, interference with the passage of air into the lungs, and by serving as a seat of infection. These disorders may be facilitated by structural defects, damaged mucous membrane, impairment of the ciliary function and the secretion of mucus, or by infection. It is important to note that damage to any part of the nasal passages may result in impairment of all other parts. Thus cessation of ciliary movement will result in a change in the character of the mucus, often followed by infection and thickening of the mucous membrane and interference with the airway. As long as there is normal ciliary function and normal production of mucus and no major mechanical interference with the airway, the whole sytem is safe with one exception. If the nasopharynx becomes the seat of a fulminating infection, the ears,

nasal mucous membrane and accessory nasal sinuses may become involved.

The real vulnerable point in the upper respiratory tract is the nasopharynx. This is true for two reasons: all air-borne organisms gaining access to the interior of the body pass through the nasopharynx and over the adenoids.

Since the discovery of the "lacteals" by Asellius in 1622, the function of the lymphatic system has been a subject of much conjecture. In 1860, Virchow first postulated the "barrier theory". This took into consideration the strategic location of lymphoid tissue throughout the body and the fact that it is almost impossible for foreign material to pass through lymph glands. In 1898, Pfeiffer and Marx demonstrated the increase in antibodies in lymphoid tissues and bone marrow after injection of heat-killed cholera bacilli into rabbits and guinea pigs (10, 11). In 1935, McMaster and Hudack (12) demonstrated the formation of agglutinins within lymph nodes. In 1939, Rich, Lewis and Wintrobe (13), in connection with studies of the body's reaction to foreign protein, stated that "... it is tempting to suspect that they (lymphoid cells) may be concerned in the same way in the process of antibody formation." In the same year Sabin (14) said that "... one may stimulate the phagocytic cells either of the liver and spleen or of the tissues and lymph nodes to produce antibodies."

Thus, over a period of several decades, there had been a gradually increasing conviction among those working in the field that the entire lymphoid system might be involved in the process of immunity (15, 16). No concrete proof of the manner and extent to which this was true existed until the work of Dougherty, Chase and White in recent years (17–21).

In 1944, these workers demonstrated in studies of extracts of tissues a concentration of antibodies in lymphocytes. In the following years a brilliant series of investigations by these workers have thrown a great deal of light on the entire subject. Working with mice and rabbits and on the basis of certain known facts about the relationship between the adrenals and lymphoid tissue, they were able to demonstrate the release of antibodies from lymphocytes. It was known that lymphoid hyperplasia occurs in Addison's disease and that adrenalectomy causes lymphoid hyperplasia in animals. Also, that adrenotrophic hormone

injected into a normal animal produces dissolution not only of the thymus but of lymphocytes in the circulating blood and lymphoid structures in general. They made extensive studies of the events which follow injection of adrenal cortical hormone or adrenotrophic hormone and came to the following conclusions: Following such injections in normal animals there occurs almost immediately a disintegration of lymphocytes, a washing out of these cells from lymphoid tissues, and extensive changes in the fixed reticular cells. Adrenotrophic hormone will produce none of these changes in the adrenalectomized animal. They were able to conclude that lymphoid tissue contributes to normal defense by:

1. Release of globulin from lymphocytes, which aids in the maintenance of blood volume.
2. Release of antibody globulin in the immunized animal.
3. Increased production of macrophages in lymphoid structures.

These workers also were able to demonstrate that the enhancement of antibody titer which follows injection of a variety of non-specific substances other than the original antigen is tied in with this same type of lymphoid tissue activity.

In 1945, Leathart (22) brought up the question of how large a role the tonsils and adenoids may play in the development of immunity, particularly in childhood, and the possible effect on this development of removal of tonsils and adenoids at an early age. It seems reasonable to assume in the face of present day knowledge that the lymphoid tissue in the upper respiratory tract may play an important role in this respect. At first glance, one would believe that the large quantity of lymphoid tissue remaining in the mucous membrane of the nasopharynx, pharynx and at the base of the tongue after the most complete tonsillectomy and adenoidectomy would suffice for these purposes. Yet, on more careful consideration, one can conceive the possibility that no matter how much lymphoid tissue remains most of it lacks the strategic location of the original tonsils and adenoids in regard to its exposure to food and air. Certainly this possibility must be carefully weighed when one is considering the removal of tonsils and adenoids in the young child simply because of recurrent upper respiratory infections. It is possible that their removal may seriously impair the child's ability to acquire immunity (23).

The tonsils and adenoids are susceptible to infection for two reasons:

1. Their surface is pitted with crypts which, in the presence of marked hypertrophy, may be deep and intricate. The epithelium lining these crypts always is either partially or totally destroyed by severe acute or oft-repeated infections and replaced with granulation tissue. The resulting scar tissue formation and the secondary keratosis, or horny overgrowth of epithelium around the orifice, interferes with drainage or completely seals off the crypt. In the tonsils this is an especially frequent occurrence and necessitates surgical removal, which must be complete and include all of the crypt system. In the adenoids and hyperplastic lymphoid nodules on the lateral and posterior pharyngeal walls and at the base of the tongue, the crypts are not so deep or branching as in the tonsils, and surgical removal of the larger surface masses, supplemented with irradiation, enables us to flatten out or completely remove the crypts without removing the underlying mucous membrane.

2. Their location exposes them to bacteria entering the mouth in food or drink and to air-borne viruses and bacteria. In the days before milk was pasteurized and before State Health Departments inspected dairy herds and killed all tuberculous cows, it was common to find tubercles in the crypts of tonsils and metastatic tuberculous glands in the neck. There is no such simple way to prevent air-borne organisms, and it is for this reason that the nasopharynx is the starting point for most virus and pyogenic upper air-passage infections and their complications.

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PATHOLOGY OF UPPER RESPIRATORY INFECTIONS

In any discussion of the treatment of hypertrophied or infected lymphoid tissue in the upper air passages, especially in children, it is of interest to review the experimental and clinical observations of the past 25 years concerning:

1. The etiology of the common cold.
2. The interaction of virus and pyogenic bacteria in producing ear and sinus complications.
3. The functions of lymphoid tissue.
4. The known causes of hyperplasia of lymphoid tissue.

Removal of tonsils and adenoids is probably the most common of all surgical procedures, and the number of patients operated on every year would, no doubt, be greatly increased if hospital beds were available to take care of the thousands of children for whom this operation is advised. It is perhaps fortunate that facilities are not available to carry out on all children the recommendation of family physicians, pediatricians, otolaryngologists and school examiners that the tonsils and adenoids be removed. It is not necessary to discuss here the indications and contra-indications for tonsillectomy and adenoidectomy, other than to say that the decision always should rest on as rational a basis for this operation as it does for an appendectomy or other surgical procedures. The end result of a tonsillectomy and adenoidectomy is good in selected cases, but in many children the benefits of the operation, even when it is thoroughly and carefully performed, are only temporary and, a few months or a year later, new symptoms begin to manifest themselves, such as impaired hearing or sinus infections. The explanation lies in the fact that lymphoid tissue is an integral part of the mucous membrane of the posterior and lateral walls of the pharynx and nasopharynx and that all of it cannot be removed. At operation only the large central mass of adenoids and smaller nodules in the fossa of Rosenmüller are taken out. Much lymphoid tissue is left behind, and as a result it not only begins to hypertrophy with the next cold but this regenerated lymphoid tissue contains crypts and crevices, similar to those in the original adenoid mass, that make ideal lodging places for virus and bacteria.

The common cold is one of the most prevalent of human diseases and

is directly or indirectly responsible for many of the conditions the otolaryngologist is called upon to treat. Epidemiological studies of the incidence of this disease show that practically every man, woman and child in the United States has, on the average, about two and one-half colds a year. Susceptibility is greatest in childhood, but continues high even to extreme old age. One of the most important portals of entry of infectious agents into the human body is the respiratory tract. In spite of such protective mechanisms as tortuous channels, an abundance of sticky mucus, ciliated epithelium and aggregations of lymphoid tissue, foreign matter, bacteria and viruses floating in the air are able to lodge in certain parts of the respiratory tract and there to set up irritative or infectious processes.

Search for the etiological agent of the common cold has extended over a period of many years. For a long time the cause was thought to be one or more of the pyogenic bacteria. This idea was dispelled by the observations that healthy individuals harbor in their nasopharynx potentially pathogenic organisms, such as pneumococcus, streptococcus, staphylococcus and H. influenzae. Usually, the first appearance of these organisms in the nasopharynx of infants is not associated with an inflammatory reaction of any kind (1). Furthermore, day by day cultures from the upper air passages of large groups of college students show that in the early days of a cold no new organisms appear in the throat flora.

In an isolated community in the far north (4), the arrival of a ship with a single individual with an acute upper respiratory infection has initiated an outbreak of the common cold, which spreads rapidly among the natives, often reaching a morbidity rate of approximately 40% in a few weeks. After the port was closed, because of ice, infection quickly died out and, in spite of extreme exposure and chilling during the winter months, there was no more acute upper respiratory disease until the following summer when communication with the outside world was again established. In this community, no significant change in the bacterial flora of the upper respiratory tract could be demonstrated during the winter when the common cold was almost unknown, and during the spring and summer when colds were most prevalent.

It was shown by Kruse, (2) in 1914, that the common cold could be communicated to experimental subjects by instilling into the nostrils

bacteria-free filtrates of nasal washings from individuals suffering from acute colds. This theory that the common cold is due to virus infection was received with scepticism, until confirmed and conclusively proven to be correct about twelve years later by Dochez and his associates (3). With a long series of carefully controlled experiments on chimpanzees and human volunteers, these observers showed that the virus initiates infection in the upper respiratory tract and produces its own type of disease. Furthermore, it seems to make local conditions in the nasopharynx favorable for secondary pyogenic infection of the surrounding mucous membrane which sometimes extends to the tonsils, sinuses, ears or lungs. In addition, repeated infections with the virus seem to facilitate the distribution of pyogenic bacteria throughout the community. The number of carriers increases and the soil is thus prepared for outbreaks of respiratory disease in the population at large.

Records of the incidence of the common cold show well-defined peaks in the early fall, mid-winter and late spring. The number of infections sufficiently severe to cause absence from work is much larger during the mid-winter and spring outbreak of colds than during the October outbreak. Kneeland and Dawes kept the infant population of a foundling home under observation for several years, studying the character of the respiratory infection in each child, its relationship to the common pathogenic organisms of the upper respiratory tract, and the changes in sensitivity of the skin reactions to products of representative strains of respiratory pathogens. In the early fall, the number of individuals giving significantly positive skin reactions to the various bacterial products was approximately 15%. As the winter progressed, the positive skin reactions became more frequent, and the intensity of the reactions increased, until in the late spring 85% of the group gave significantly positive skin reactions to the pneumococcus, streptococcus and H. influenzae. The incidence of pathogenic organisms found by culture varied from time to time. During one year, the carrier rate for H. influenzae was high. During the preceding year the carrier rate of pneumococcus rose to the exceedingly high figure of 95%. Throughout the period of widespread distribution of pathogenic organisms, acute upper respiratory infection was usually severe and there was a marked increase in the number of diagnoses of grippe, influenza, pneumonia and their complications, and a corresponding decrease in the

number of diagnoses of common cold. On the other hand, when the distribution of pathogenic organisms was relatively limited, as shown by daily cultures, the great majority of acute upper respiratory infections received the diagnosis of common cold. The conclusion seems justified that certain epidemics of the severe forms of respiratory infection result from the coincidence of an outbreak of the common cold with a period of widespread distribution of well-recognized pathogenic organisms of the respiratory tract.

The nasopharynx is the most important portal of entry of infectious agents in the upper air passages. Pathogenic organisms gaining entrance to the body by way of the respiratory tract fall into two large groups, one of these causes varying degrees of inflammatory reaction in the respiratory organs in the early stages of the disease, to be followed later by evidence of disease in organs distant and unrelated to the respiratory apparatus. Types of such diseases are measles, cerebrospinal meningitis, rheumatic fever, hemorrhagic nephritis and others. The second large group may be called the true respiratory diseases in which the inflammatory process is more or less confined to the respiratory tract itself.

The common cold virus can be grown by inoculating tissue cultures or living chick embryos. The cultures are incubated under anaerobic conditions at 37° Centigrade, and transfers are made to fresh tissue medium every three or four days. The virus will not grow under aerobic conditions. The different generations of virus grown in this way have been inoculated into human volunteers from time to time and have produced typical colds in over 50% of the individuals inoculated. The common cold virus, in common with all other viruses, grows only in living tissue; it differs from bacteria in that it will not grow on dead tissue. The virus must enter a living cell before it can multiply and cause clinical symptoms. The chimpanzee is the only animal known to be susceptible to the common cold virus. Symptoms usually manifest themselves from 24 to 48 hours after intranasal inoculation with the virus, both in chimpanzees and human volunteers. The first subjective symptom complained of by the volunteers is a "hot spot" in the nasopharynx, nasal obstruction, sneezing and abundant mucous discharge. Virus infection never causes a purulent discharge. Then follow hyperaemia of the pharynx mucosa and swelling of lymphoid

tissue. Secondary bacterial invasion and purulent discharge usually come in the later stages of the cold. The virus, together with the hyperaemia, edema and increased secretion of thick mucus, seems to promote and further a pyogenic infection of the ears, sinuses and other parts of the respiratory tract. All evidence suggests that the bacteria of the upper respiratory tract are of themselves powerless to initiate infection (4) (5).

We do not know the mechanism by which the virus enters a cell, but we do know that the virus must be in contact with the cell for at least 30 minutes before it gains entrance or is able to produce symptoms. In what part of the upper respiratory tract does the virus find a lodging place for a sufficient length of time to allow it to enter cells and begin to multiply? Why are some children and some adults more susceptible to colds than others? The explanation must be largely mechanical. Certainly it is not due to an acquired or induced immunity to the common cold. The primary object of all investigators of the common cold has been to find a vaccine, drug or some measure that will prevent or protect against colds, and so far all efforts in this direction have been a failure. Many large studies, carefully conducted with adequate controls, have shown no real difference in the incidence of colds following the use of stock bacterial vaccine, autogenous bacterial vaccine, or subcutaneous injections, at weekly intervals, of the common cold virus grown in tissue culture and from time to time passed through apes or volunteers (5).

Antibiotics and sulfonamides control the acute bacterial complications of the common cold but have no effect on the virus and will not prevent recurrences. Based on the findings of early investigators that chronic respiratory disease of rats on a diet deficient in Vitamin A could readily be cured by feeding Vitamin A, large amounts of Vitamins A and later D and B have been given to children, but it was found that in general they fared no better in regard to the occurrence of respiratory disease than do those on an ordinary diet. In addition to its antirachitic properties, ultraviolet light has been proposed as an aid to general health, and this agent has also been tried as a prophylactic measure against colds. Well controlled studies on this subject on a large group of college students indicate that regular exposure to ultraviolet rays does not diminish the incidence of colds. Experiments on

college students have also shown that neither hygienic sleeping conditions, the kind of clothing worn, or an abundance of out-door exercise have any appreciable effect in lessening susceptibility to the common cold or increasing the resistance to respiratory infections (6).

Following surgical removal of tonsils and adenoids in children, however, otolaryngologists and pediatricians have repeatedly observed a marked diminution and, in some cases for the period of a year, an almost complete absence of colds. This fact also suggests a mechanical factor in the cause of upper respiratory infections. Reports in the literature indicate that there is no statistically significant decrease in the incidence, severity, and type of upper respiratory infections after removal of tonsils and adenoids. Such studies, however, have failed to take into account the tendency for lymphoid tissue to regenerate. The mucosa of the posterior and lateral walls of the pharynx, and especially that of the nasopharynx, is rich in lymphoid tissue. Indeed lymphoid tissue is an integral part of the mucous membrane in these regions, and for this reason it is impossible to remove all of it surgically. In a group of 1365 school children examined with a nasopharyngoscope, 755 had had their tonsils and adenoids removed at various hospitals in Baltimore. As a rule, the tonsils had been cleanly removed, and in many the oropharynx looked normal, but in more than 75% adenoid tissue had recurred in the nasopharynx (7). We have no data regarding the incidence of colds before and after operation in this group, but mention these observations in order to emphasize that recurrence in the nasopharynx after operation is not only frequent, but that the regenerated lymphoid tissue usually contains crypts and folds similar to those seen in normal adenoids. As will be shown later, these crypts and folds make ideal lodging places for air borne viruses and bacteria and are probably of prime importance in the epidemiology of upper respiratory infection.

Lymphoid tissue is one of the three important protective mechanisms in the upper air passages. The other two are: 1) the layer of mucus that is constantly being secreted by the nasal mucosa, and 2) ciliated epithelium that keeps this layer of mucus moving backward into the nasopharynx and pharynx, where it is joined by saliva from the mouth, finally flowing into the esophagus. Lymphoid tissue is most abundant in the midline of the nasopharynx and in the fossa of Rosenmüller,

but after surgical removal of adenoids in children nodules of this tissue often appear in and around the pharyngeal orifice of the eustachian tubes, in the choanae near the posterior end of the middle turbinates, and on the posterior and lateral surfaces of the vomer. These facts concerning the distribution of lymphoid tissue in the nasopharynx and posterior part of the nose are important for a clear understanding of recurring colds, of certain types of impaired hearing, attacks of suppurative otitis media and mastoiditis, ethmoiditis and chronic post-nasal discharge.

We speak loosely of acute tonsillitis and nasopharyngitis as an infection of lymphoid tissue, but histologic examination of tonsils and adenoids that have been removed soon after an acute infection rarely shows an abscess or even any large number of polymorphonuclear leucocytes or bacteria in the lymphoid tissue itself. The most prominent changes are seen in the crypts, where the lining epithelium is partially or completely destroyed (8). Lymphoid tissue itself is very resistant to infection by the common pyogenic bacteria. It is often invaded and destroyed by the tubercle bacillus, the typhoid bacillus and a few other organisms. The chief functions of lymphoid tissue are to protect against pyogenic invasion and to aid in the manufacture of antibodies. This is probably the reason why there is so much lymphoid tissue in the mucous membrane of the nasopharynx and pharynx and in the intestines, the two areas most exposed to bacterial invasion.

The life cycle of the lymphocyte is short, and Dougherty and White have shown that by dissolution they contribute proteid (serum gamma globulin) to the blood and thus help to maintain blood volume. This normal dissolution process is under adrenal cortical control. In adrenalectomized animals, lymphoid tissue throughout the body hypertrophies because the normal dissolution process is slowed or stopped. On the other hand, injection of adrenal cortical hormone in a normal animal accelerates disintegration of lymphoid tissue, and within an hour degenerative changes are seen in germinal center cells, and lymphocytes rapidly disappear from the blood. These changes prevent replacement of lymphocytes as they are used up, and lymphoid tissue throughout the body atrophies. Alterations in lymphoid tissue do not occur following similar injections in adrenalectomized animals. It is probable that infection stimulates the formation of adrenal cortical

hormone, which in turn greatly increases the disintegration of lymphocytes, thus releasing antibody globulin (9). These facts integrate the role of lymphocytes and adrenal cortex in the normal and pathological physiology of the organism, and clearly indicate that lymphoid tissue in the upper air passages, as elsewhere in the body, has a function. When hypertrophied or infected, therapy should cure the patient and prevent recurrence of symptoms, but should be as conservative as possible so far as removal or destruction of normal lymphoid tissue is concerned.

The common cold virus usually is air borne, but before it can produce symptoms it must find a lodging place in the upper air passages and remain undisturbed by the flow of mucus and in contact with a cell for at least 30 minutes. Experimental studies indicate that this length of time or more, is necessary for the virus to enter living cells and begin to multiply and produce symptoms. Clinical observations suggest that the virus lodges in crypts and crevices in adenoids and in the hyperplastic nodules of lymphoid tissue that almost invariably appear in the nasopharynx after surgical removal of tonsils and adenoids. We have repeatedly seen children operated on for recurring upper respiratory infections who were entirely free of colds for six months or a year after the operation. When these patients again begin to have frequent colds, examination with a nasopharyngoscope usually shows nodules of lymphoid tissue in the nasopharynx. These nodules contain crypts, and evidence that these crypts are serving as a portal of entry for the virus is furnished by the marked decrease in the number and severity of colds that follows a course of irradiation treatments of the nasopharynx. Irradiation (10) acts on germinal center cells (Fig. 2), stops mitosis and the formation of new lymphocytes to replace those that are constantly being lost by the normal dissolution process—thus causing the hyperplastic nodules of lymphoid tissue gradually to shrink and disappear, obliterating the crypts and leaving in their place smooth, normal-looking mucous membrane and no favorable places for the virus to lodge and grow in the nasopharynx.

Many careful studies of large groups of individuals have shown that streptococcus, pneumococcus or H. influenzae may be present in the nasopharynx for long periods without signs or symptoms of infection. These organisms grow in the crypts and crevices of lymphoid tissue in

the nasopharynx as they would in a test tube. An acute upper respiratory infection, due to the common cold virus, activates these bacteria and possibly increases their virulence. This is the probable explanation for the ear, sinus and bronchial complications of a cold. These bacterial complications of a cold can be cured in the acute stage by the administration of sulfonamides and antibiotics. It is possible with these drugs to clear temporarily the upper air passages of gram positive bacteria. If the drug treatment is prolonged and intensive, the gram positive pathogens disappear but are replaced with gram negative organisms, the most common being the colon, proteus and Friedlander bacilli. These in turn are activated by recurring virus infections, the ear, sinus and bronchial complications recur but this time with gram negative organisms. Streptomycin and penicillin, either separately or in combination, may be essential but certainly are only a part of the treatment. It is impossible to free permanently the upper air passages of bacteria, but if these bacteria are relatively harmless until activated by virus infections, and the principal area in which the virus lodges and begins to grow is the nasopharynx, it is obvious that, in order to lessen or obviate virus infections, we must supplement the drug treatment by removing the crypts and crevices in nasopharyngeal lymphoid tissue with operation and irradiation.

IRRADIATION OF ADENOIDS

It is for these reasons that we urge otolaryngologists to concentrate their attention on the nasopharynx. If symptoms improve following operation or irradiation, we must realize that neither of these measures remove all lymphoid tissue in the nasopharynx. It may regenerate in the fossa of Rosenmüller, on the posterior part of the septum and in the choanae, and symptoms recur. Therefore, the patient should be examined with a nasopharyngoscope at least once a year, preferably during the summer months, and, if necessary, further irradiation given to tide him over the winter months. In this way we feel sure we can prevent in many children impaired hearing due to eustachian tube obstruction or suppurative otitis media, recurring infection of the nasal sinuses, and, in selected cases, lessen the severity and frequency of bronchial asthma attacks (11).

It has long been the custom of the family physician, the pediatrician,

school doctors and otolaryngologists to advise removal of tonsils and adenoids because they are hypertrophied and interfere with speech and nasal breathing, or because the children have repeated upper respiratory infections, with or without some of the pyogenic complications. Of course it is necessary to relieve symptoms and restore the child to health, but we doubt that many of the tonsillectomies now being done are necessary or advisable. This conclusion is based on the results of irradiation of the nasopharynx in the out-patient department of The Johns Hopkins Hospital during the past ten years.

Up to this time, we had used irradiation therapy almost exclusively for the treatment of certain types of impaired hearing. During the depression years, preceding the outbreak of war, the hospital found it increasingly difficult to furnish free beds. It was then we began to treat the nasopharynx with radium for complaints which we previously had thought justified operative removal of tonsils and adenoids. We were forced to treat only the nasopharynx because it is not safe for the doctor to hold a radium applicator in his hand and apply it to the tonsils or to hyperplastic lymphoid tissue in the pharynx. When irradiating the nasopharynx, the patient lies on a couch and the doctor passes the applicator along the floor of the nose until it is in contact with the lymphoid nodules he wishes to remove. He then withdraws to a safe distance. Our previous experiences in treating patients with various types of ear disorders had suggested that the nasopharynx is the primary seat in most upper air passage infections, but we had not expected the beneficial results that soon became apparent in this group of ambulant patients. Acute infection of the accessory nasal sinuses, ears, and tonsils can be cured easily with antibiotics or sulfonamides, together with local measures that promote drainage; but so long as the adenoids with their crypts and crevices remain, conditions are favorable for subsequent pyogenic infections, initiated by the common cold virus, which again may spread to the ears, sinuses or tonsils. As patient after patient with recurrent acute attacks and, in some cases, with chronic infection of the ears and sinuses got well and remained well under this combination type of treatment, the number of patients treated in the radium clinic of the out-patient department was increased. For several years from 50 to 75 patients have been treated each week with results on the average far better than those previously

obtained from operation. To get good results, however, the patients must be carefully selected. Usually the first few infections of the middle ear, sinuses, and tonsils do not leave permanent changes in the lining mucosa or epithelium in the crypts, but after repeated acute infections irreversible changes occur that mechanically interfere with drainage, and surgery becomes a necessary part of the treatment.

Aside from selection of suitable cases, two other factors contribute to the success of this type of treatment. Irradiation in the proper amount and at the proper intervals shrinks lymphoid nodules on the posterior part of the septum, in the choanae near the posterior end of the middle turbinate, and around the orifice of the eustachian tubes, all locations inaccessible to surgical removal. If the dosage is increased, all lymphoid tissue in the nasopharynx can be permanently removed, but excessive dosage always is followed by the appearance of telangiectases in the mucous membrane and dryness and crust formation in the nasopharynx, which are neither necessary nor desirable. A course of five treatments at two week intervals with the smaller dosage, (8½ minutes on each side) with the 50 milligram 0.3 mm. monel metal radium applicator, or three treatments with the maximum dosage of 12 minutes on each side at two week intervals, has the desired effect and may be repeated with safety once a year if symptoms recur. This leads to the second factor that contributes to success in controlling the incidence of colds and their complications. After every operation or irradiation of the nasopharynx, the patient must be followed and examined at least once a year for several years, and every effort made to keep the upper air passages in good condition, just as the dentist examines his patients at regular intervals in order to keep the teeth in good condition.

Observations on these dispensary patients, on a large group of school children, and on several hundred private patients, confirmed and strengthened our impression that removal of infected adenoid tissue will prevent recurring colds and their complications more effectively than any of the measures cited above. Often irradiation is all that is required, but sometimes the combination of surgical removal, supplemented with antibiotics and irradiation, is necessary to get the best results. The primary object of our study of school children (7) was to determine the relation of hyperplastic lymphoid tissue in and around

the orifice of the eustachian tubes to impaired hearing. All children were tested individually in a sound-proof room with the voice, audiometer, and tuning forks, and then examined with a nasopharyngoscope. In those found to have hearing impairment every effort was made to maintain the nasopharynx in as near normal condition as possible. Others who were similarly examined and found to have hypertrophied lymphoid tissue but no hearing impairment were not irradiated and served as controls. For two years examinations and tests were made at frequent intervals. Then followed a period of four years, during the war, when they were not seen. In 1946 we were able to trace and re-examine 600 of the original 1365 children. This group contained both controls and treated cases. The hearing was found to be improved, with return of threshold acuity for all tones to normal or near normal in somewhat more than half of the treated children, who had had a 25 to 35 decibel loss for all tones. In 1939, when first seen, most of these 600 children gave a history of frequent colds. When questioned in 1946 regarding their susceptibility to colds and sore throats, the terms "rarely", "never", "once a year", "two years since the last one", "mild when I have one now", "they last only a few days", etc. were used far more often by those in the treated group than by those in the control group who had had no treatment.

If nodules of lymphoid tissue are seen in the fossa of Rosenmüller, in the choanae and on the posterior part of the septum, the patient's history almost invariably indicates that upper respiratory infections are frequent, often with ear, sinus or other complications. On the contrary, if no lymphoid tissue is seen in these locations, colds are usually infrequent, mild, and rarely cause loss of time from work or school. Examination with a nasopharyngoscope is necessary in order to visualize these areas. It is not the size but the location and contour of lymphoid tissue that is important. Lymphoid tissue in these critical areas is inaccessible to surgical removal. The presence of a small mass of adenoids in the midline of the nasopharynx has but little effect on the incidence of colds. The important areas are the choanae and the lateral walls of the nasopharynx. Nasopharyngoscopic examination of a patient with a coryza or sinus infection shows a stream of discharge flowing from the choanae into the fossa of Rosenmüller, not into the midline of the nasopharynx (Fig. 1). If this is the

normal pathway of the flow of mucus from the nose into the nasopharynx, it is easy to understand how the virus finds a lodging place in the crypts of lymphoid tissue in these areas; why colds recur when

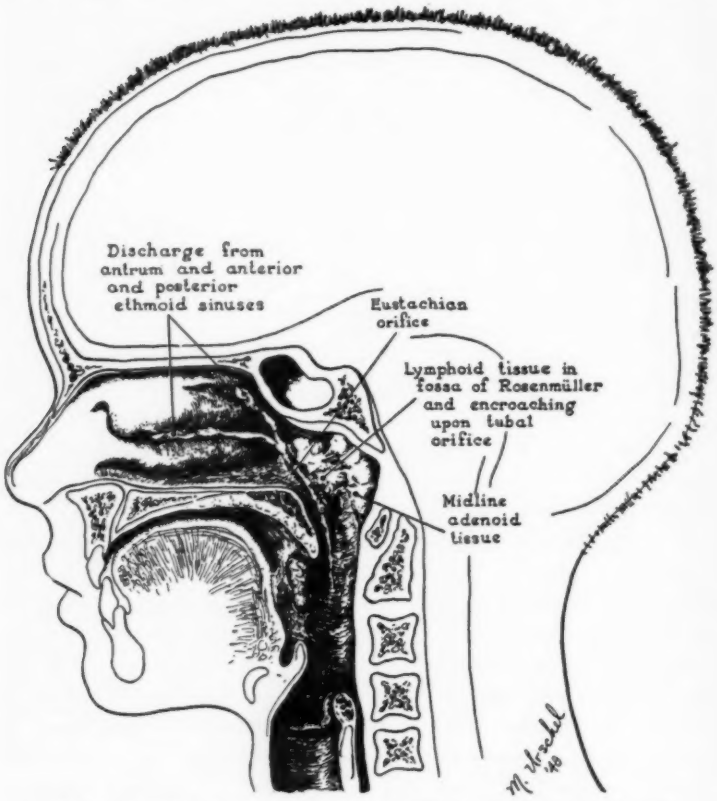

Discharge from antrum and anterior and posterior ethmoid sinuses
Eustachian orifice
Lymphoid tissue in fossa of Rosenmüller and encroaching upon tubal orifice
Midline adenoid tissue

FIG. 1. Drawing showing anatomical relationships of the nasopharynx

hyperplastic nodules appear in these areas after removal of tonsils and adenoids; and why colds become less frequent or entirely cease if lymphoid tissue in these areas is kept down with irradiation.

The tonsils and adenoids should be removed surgically if the patient has repeated attacks of tonsillitis. Hyperplastic nodules of lymphoid

tissue, which often appear on the posterior and lateral walls of the pharynx after this operation, may also have to be removed surgically if they become chronically infected, especially if the patient has a severe cough and asthmatic bronchitis following every cold. The mere presence of a "granular pharyngitis" however does not always demand operation, cauterization, or other forms of local treatment. Often the symptoms may be greatly improved or entirely cured in these cases by irradiation of the nasopharynx alone. If symptoms recur, a second or third course of irradiation may be given with safety, provided the proper dosage and intervals between courses are observed. Irradiation of the nasopharynx may thus be used to tide a child over a difficult period. Antibiotics are used to cure the acute manifestations, but irradiation is used to remove the underlying cause of upper air passage infections. The combination prevents recurrences and thus aids in obtaining a permanent cure.

The impression we wish to convey in this publication is that irradiation of the nasopharynx with a radium applicator is no panacea, but in selected cases it is an invaluable therapeutic measure. Anyone who has had a series of common cold infections knows that they do not always begin with a nasopharyngitis. Sometimes the virus gains entrance through the nasal mucosa, injures cell membranes, and thus prepares the way for secondary bacterial invasion. There is abundant evidence, however, that the more severe types, with complications, begin in the nasopharynx. The acute symptoms can be controlled with anti-bacterial drugs, but to prevent recurrent infections and the possibility of permanent injury to ear and sinus mucosa, hyperplastic nodules of lymphoid tissue in the fossa of Rosenmüller, in the choanae, on the posterior and lateral surfaces of the vomer, and in and around the orifice of the eustachian tubes must be searched for and irradiated—not excessively, but enough to keep them small and as free as possible from infection.

Before discussing the technique of irradiation with the nasopharyngeal radium applicator it is profitable to review some of the general factors in irradiation therapy (12).

X-rays and gamma rays of radium, rays of ordinary visible light, ultra-violet and infra-red rays, as well as radio waves, are similar in many respects. They all have the same speed, 186,000 miles per

second. They have no electrical charge. They can be polarized, reflected and diffracted. The only difference is their frequency or wave length. The shortest wave lengths are obtained from the gamma waves of radium and from extremely high voltage x-ray. There is a direct relationship between wave length and energy; the shorter the wave length, the greater the energy, i.e., the penetrating power.

Beta rays vary greatly as to speed. Some closely approach that of light. Approximately 93 per cent of the beta ray output of an applicator is absorbed by one centimeter of tissue. For this reason beta rays are valuable in treating many superficial conditions on the skin, in the nasopharynx, and the eye. A different type of applicator (screen), however, is used in each of these locations. The 0.3 mm. monel metal radium applicator is designed for the treatment of hyperplastic lymphoid tissue in the nasopharynx, and is not suitable for the treatment of malignant growths in the nasopharynx or nose, or benign lesions of the skin or conjunctiva.

When high penetration is desired it is very important to remove by filtration all beta rays. Gamma rays from radium have a capacity of penetrating tissues (many pass entirely through the body) and great thicknesses of very dense metals; for example, a small percentage of these rays pass through 12 inches of lead. It is for this reason that office personnel should not sit day after day at a desk in close proximity to a radium applicator, even though it is in its lead container. Always remember that distance affords the greatest protection for the doctor and his helpers.

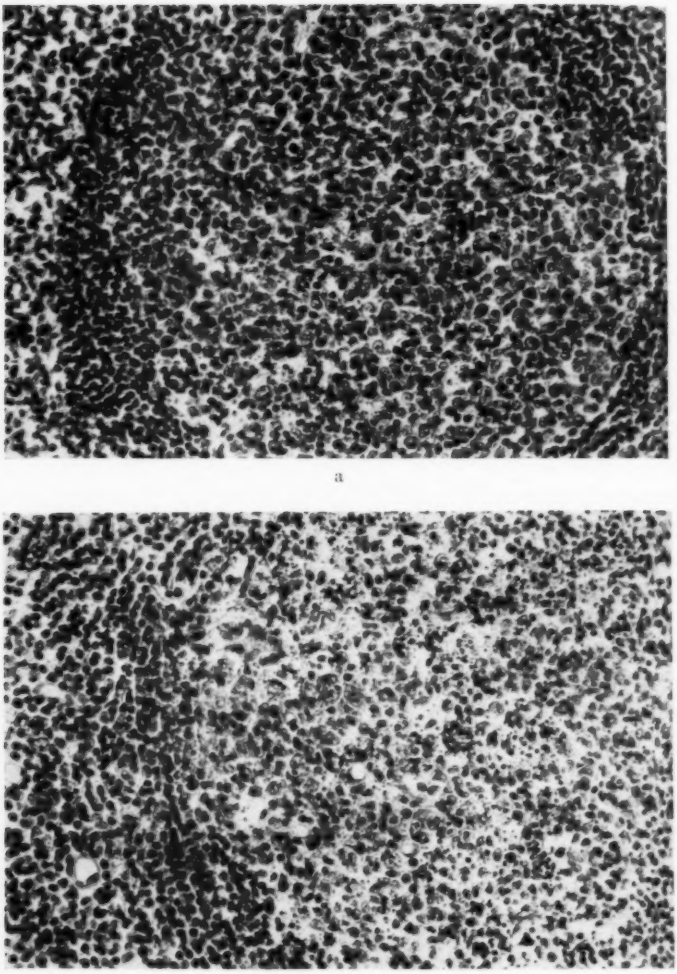
The rays from radon and radium are identical. Irradiation may be so weak that no demonstrable changes in cells or tissues can be observed. It may be so strong that all cells and tissues it strikes may be completely destroyed. Therapeutic irradiation lies between these two extremes. What a metal filter does is to remove the longer wave lengths completely. It is obvious that this reduces the quantity of rays, but increases the penetration, due to the fact that the average wave length is shorter. Some of the rays pass through the body unchanged; these have no biological effect. It is practically certain that the rays which are absorbed, whether in whole or in part, produce ions and that these ions cause the biological changes in tissues. Both clinical and experimental observations indicate that irradiation is

always an injurious agent and never a direct stimulant. It is true that radiation, which is not lethal and the recovery rapid, may be followed by overactivity in growth, but this is not peculiar to irradiation since it often follows other types of injury. The effects are quite different as the time of exposure is varied. A given amount of irradiation, delivered in a few minutes, may produce a violent reaction on the skin or mucous membrane, whereas if the same amount be given in a period of a month, no reaction will occur. It is certain that it is much better to treat nasopharyngeal lymphoid tissue with three or four doses (just short of the irritating or destructive level), at intervals of two weeks, than by a single massive dose.

The changes, both gross and microscopic, which take place in cells and tissues after irradiation, are not specific and are observed following various other injuries. Following irradiation, the first changes are seen in the nucleus of the cells. (Fig. 2) Mitosis and cell division are brought to a halt. The protoplasm of the cell body soon becomes granular. With the ideal irradiation the cell is not destroyed, even cell life is not shortened, but reproduction is prevented. We should strive to get this effect in treating the nasopharynx.

There are great variations in radiosensitivity between different cells and tissues, and indeed individual cells of the same type vary greatly. Moderate irradiation may destroy half or more of the cells of a given tissue, but to destroy every cell may require four or five times the amount of radiation. There is evidence that tissue in the nasopharynx, as elsewhere in the body, plays a role in antibody production and is to be preserved so far as possible. There is also evidence that recurring infections of tonsils and adenoids are due in part to the crypts and crevices in which viruses gain entrance and bacteria lodge and grow. If the contour can be sufficiently changed to flatten out these recesses with operation or irradiation, and at the same time preserve as much lymphoid tissue as possible, infections often become less frequent and less severe and the end result is more ideal than that which follows total removal or destruction of all lymphoid tissue.

The "latent period" is the term applied to the time that elapses after irradiation before definite local reaction changes can be seen. The length of the latent period varies inversely with the intensity of the irradiation. In the skin, slight erythema may occur as late as three



a

b

FIG. 2. Irradiation of the nasopharynx with the dosage used does not cause an immediate change in the gross or microscopic appearance of any of its tissues. Sections of adenoids removed 10 minutes after irradiation (a) cannot be told from sections of untreated adenoids. When removed, 24 hours after irradiation the germinal centers of the lymphoid nodules show a marked degree of fragmentation of the rapidly multiplying cells. (b) All other tissues, including the vascular endothelium, are normal in appearance. Magnification of 450 diameter.

weeks after mild radiation, whereas with very intense radiation it may develop in a few hours. These changes involve both the nucleus and the cell body. Physiologic changes are more difficult to evaluate, but a definite change in metabolism, increased permeability of cell membranes leading to edema, and increased acidity are all common occurrences.

The aim of irradiation treatment always is to cure and not to injure the patient. In ophthalmology it is particularly vital not to injure any of the essential structures of the eye upon which vision depends. In nose and throat work, injury of bone, cartilage and nerve tissues must be avoided, and the dosage is planned so as to reduce to a minimum the possibility of such injuries. In otolaryngology and ophthalmology the beta ray applicators are particularly valuable in treating superficial lesions. For the treatment of deep-seated and extensive (malignant) lesions such as may occur in the orbit, sinuses, nasopharynx, pharynx, tonsils or larynx, x-ray is the best agent. In using x-ray for this purpose accurate cross-firing through small portals is essential. Far too frequently portals 10 centimeters in diameter are used in treating a growth 1 centimeter in diameter. This inevitably means over-irradiation of the surrounding normal tissues.

The technical details of treatment with beta ray applicators are simple. After a short course of instruction any competent ophthalmologist or otolaryngologist can safely and effectively use these applicators on his patients. The course of instruction should include training in the out-patient department in the diagnosis of the various conditions that may be benefitted by this type of treatment, and, under supervision, the actual treatment of patients. Malignant growths, however, should always be treated by the radiologist.

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CLINICAL CONSIDERATIONS

Lymphoid tissue in the pharynx and nasopharynx plays an important part in both the physiology and pathology of the upper air passages. It protects against invasion of the body by pyogenic bacteria, but affords no protection whatsoever against the common cold virus. On the contrary, the crypts of lymphoid tissue, especially in the nasopharynx, make an ideal lodging place and portal of entry for this particular type of virus. The virus damages cell membranes and opens a pathway for bacterial infection, which is directly or indirectly the cause of impaired hearing, sinus infection and a host of other conditions the otolaryngologist is called upon to treat. The physician must not be satisfied merely to restore the hearing, relieve the pain or stop the discharge of acute infections, especially those in the ears and sinuses, but following recovery from the acute symptoms a search must be made for any abnormality in the nasopharynx and upper air passages that might cause a recurrence of the ear or sinus complications with the next cold. In other words, every effort must be made to prevent disability due to imparied hearing, chronic infection of the accessory nasal sinuses and bronchiectasis. The therapeutic measures available include surgical measures and vasoconstrictors to insure adequate drainage, the administration of sulfonamides or antibiotics to combat the acute infection, and surgical operation, irradiation, or both, in an effort to prevent recurrence. The rationale for this lies in the remarkable ability of the mucous membrane in the ears, sinuses and bronchi to return to normal after an acute infection; oft-repeated infections, however, lead to chronic changes in the lining mucous membrane of ears and sinuses that permanently interfere with drainage and necessitate radical surgical operation. Our experience indicates that much good can be accomplished by preventive therapy in children, but if impaired hearing,

due to intermittent blockage of the eustachian tubes, or recurrent sinusitis is not corrected and stopped during childhood, when most of these maladies begin and the changes in the mucous membrane are still reversible, there is little likelihood of curing them in adults.

We began in 1924 to use irradiation with a radon applicator for the removal of recurrent lymphoid tissue following adenoidectomy, and particularly for displaced nodules of lymphoid tissue in and around the pharyngeal orifice of the eustachian tubes that often lead to impaired hearing. These treatments proved so effective and so simple and safe that we have used this type of therapy in selected cases with increasing confidence and satisfaction for 24 years. The late Dr. Curtis F. Burnam, one of the outstanding authorities on the physics of radium and its clinical uses, was from the beginning the radiological consultant for this work. He has been responsible for all decisions as to dosage, type of filtration, and construction of applicators (1). During this period applicators with various types of filtration have been used—gold, brass, aluminum and monel metal. Determination of the proper dosage for these various types of applicators (i.e. the number of minutes the applicator must remain in contact with the tissue being treated) was of the utmost importance to insure safety and effective results. The dosage we used was not established by mathematical calculations, but by determining the erythema dose of the applicator for buccal mucous membrane. Less than half the erythema dose has always been used in treating nasopharyngeal lymphoid tissue. The clinical results have been satisfactory with this dosage; no complications have arisen, and we are certain that a larger dose is neither necessary nor desirable.

For many years the interval between treatments was one month and most patients were given three treatments of 2 to 2.2 gram minutes through 1 mm. of brass. Only in exceptional cases were more than three treatments given in one year, and then only after consultation with an expert radiologist. During the war years, when it became necessary to speed up the treatments, the interval between each treatment was reduced to three weeks and later to two weeks. These changes were based on observations with the nasopharyngoscope of the reaction following each treatment and how long it persisted. These observations were made on several hundred patients.

As the value of nasopharyngeal irradiation, in the treatment of various conditions that arise from hyperplastic or infected lymphoid tissue, became more and more apparent, inquiries began to come from those engaged in Public Health work among children in rural districts about the possibility of substituting nasopharyngeal irradiation in selected cases for surgical removal of tonsils and adenoids. These inquiries and the demands of the Army Air Forces and Submarine Training School during the early days of the war for some simple way to remove lymphoid nodules in and around the pharyngeal orifice of the eustachian tubes, in an effort to prevent aerotitis, led to the development of the 50 mg. radium applicator, screened with 0.3 m.m. of monel metal. (Fig. 3) This applicator utilizes to the full the large beta ray out-put that is made possible by the monel metal screen. Only rays that are absorbed by cells are of therapeutic value; those that pass through the

FIG. 3. Photograph of the Monel Metal Radium Applicator

body are of no value in treatment. Practically all beta rays are absorbed in the first 10 m.m. of tissue, and since nasopharyngeal lymphoid tissue is superficial, the 50 mg. 0.3 m.m. monel metal applicator is a satisfactory therapeutic instrument for this area. Gamma rays penetrate to great distances and, like high voltage x-rays, are used to treat deep-seated malignant growths. If platinum or gold replaced monel metal as a screen on the 50 mg. radium applicator, the time of each treatment would be greatly prolonged—from 12 minutes on each side of the nasopharynx for the monel applicator to well over an hour on each side of the nasopharynx for the platinum or gold screen. A 1 m.m. aluminum filter allows the passage of a larger percentage of beta rays than do any of the other metals we have tried, but it is less durable and dependable than monel metal. The applicator becomes practically inert, if even a tiny hole appears in the wall of the radium-containing chamber. The radium-containing chamber must be hermetically sealed, since the first by-product of radium dissolution is radon, and therapeutic beta and gamma rays are formed only from radon. It is evident that if the radon escapes from the radium-con-

taining chamber, no beta and gamma rays will be generated within the applicator and it will be useless.

The present applicator has a radioactive length of 15 mm., thus covering the area from a point just anterior to the tubal orifice back to the fossa of Rosenmüller with the applicator in one position.

At first, the dosage time for the 0.3 m.m. monel metal 50 mg. radium sulphate applicator was exactly comparable to that of the 50 mc. radon applicator with the same type and thickness of screen, but later it was learned that the radium salt itself acted as an additional filter and the dosage time had to be adjusted accordingly. At present, the technique of treatment with this applicator is as follows:

1. The applicators are stored in a cylindrical lead block with 3 inches (7.5 cm.) of lead on all sides.

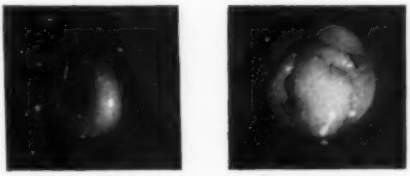

FIG. 4. Nasopharyngoscopic photographs showing appearance of normal tubal orifice and tubal orifice partially overgrown with adenoid tissue.

2. The nose and nasopharynx have been previously examined with a nasopharyngoscope to determine the suitability of the patient for radiation treatment (Fig. 4).

3. The floor of the nose is anesthetized by the passage of a fine cotton applicator moistened with a few drops of 20% cocaine. In most instances this is unnecessary as the placing of the applicator occasions little or no discomfort. Local anesthesia is chiefly of value in very apprehensive patients or those with severe nasal obstructions.

4. With the patient recumbent, one radium applicator is passed into the nasopharynx on each side of the nose until the end lies against (Fig. 5) the posterior nasopharyngeal wall in the fossa of Rosenmüller (Fig. 6).

5. A timing clock is set for 12 minutes (1 gm. 36 sec. equivalent) and the physician goes to a distance of about 20 feet.

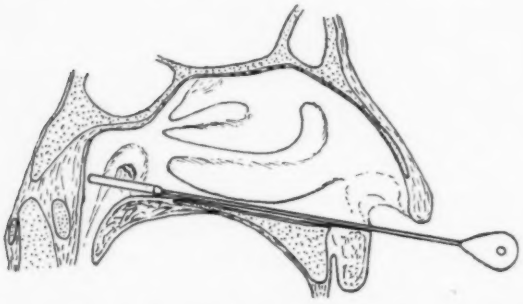

FIG. 5. Cross section to show position of radium applicator in nasopharynx

FIG. 6. Photograph of child during treatment with applicator in position

6. When the alarm rings, both applicators are removed and quickly cleansed with some automatic cleaning device and immediately replaced in the lead block. The applicators must never be sterilized

with heat. Under no condition is the radium-containing capsule ever touched with the fingers.

7. Two additional treatments are given at intervals of two weeks.

8. Children are followed with periodic examinations at the end of six months, and after that at least once a year. The course of treatment may be repeated once or twice at intervals of one year if symptoms recur.

This technique is so simple that it can be mastered easily by any physician and is perfectly safe as long as the rules are strictly followed. On the other hand, the selection of cases in need of this treatment must be based on careful clinical judgment, after thorough study of the patient's history and examination of the ears, nose and throat, including nasopharyngoscopic examination.

It is for this reason that we believe the treatment is best carried out by the otolaryngologist rather than the radiologist.

It is impossible to eradicate completely the nasopharyngeal lymphoid tissue by surgery, because lymphoid tissue is an integral part of the mucous membrane of the nasopharynx. This lymphoid tissue is exceedingly susceptible to hyperplasia under the stimulus of infection or allergy. Irradiation offers a simple non-surgical method of reducing the size of lymphoid nodules.

Although our first interest in this form of treatment was aroused by the dramatic improvement in hearing which occurred in some children following treatment, our experiences during the past 24 years have demonstrated its usefulness in selected cases with the following conditions:

1. Hearing impairment thought to be partially or wholly on the basis of chronic or recurrent eustachian tube obstruction.

2. Chronic otitis media when the concurrent chronic mastoiditis is properly handled.

3. Recurrent acute attacks of otitis media.

4. Recurrent acute attacks of sinusitis.

5. Recurrent acute attacks of pharyngitis or tonsillitis when the infection begins in the nasopharynx.

6. Recurrent colds in selected cases.

7. Bronchitis secondary to upper respiratory infections.

8. Certain patients with bronchial asthma.

9. Aerotitis (2–5).

10. In some patients with postnasal discharge, tinnitus, fullness in the middle ear, etc.

In all of these conditions, the symptom is the primary consideration. The secondary consideration is whether or not the nasopharyngeal and other examinations confirm the suspicion that the primary focus of infection is in the nasopharyngeal lymphoid tissue. Adenoids are not irradiated unless the patient suffers from symptoms thought to be attributable to them; nor are patients irradiated for symptoms unless there is evidence of the presence of infected adenoid tissue.

If the adenoids are very large they should be removed surgically before irradiation. If there is chronic tonsillitis, sinusitis or mastoiditis these must be treated before or simultaneously with irradiation of the adenoid tissue. Before leaving this section, it would be well to stress the following essential points:

1. In many patients, surgical adenoidectomy alone is not an adequate answer to the problem of infected adenoids.

2. Lymphoid tissue is highly sensitive to irradiation and may be satisfactorily reduced by doses which will not harm the surrounding tissues.

3. This may be accomplished safely and without complications by a method which has been used by us for a quarter of a century.

4. In order to determine those who are in need of therapy, nothing can substitute for careful examination of the nasopharynx with the nasopharyngoscope.

5. Radium therapy of any kind is potentially dangerous, and if one is to avoid all risk to the patient the above rules as to dosage, number of treatments and repetition of treatments must be strictly followed.

RESULTS

It has never been feasible to study an adequate series of controls, because the efficacy of the therapy was apparent in some conditions from the beginning. As a result, any evaluation of the usefulness of irradiation therapy, in alleviating such clinical conditions as those described above, must be based on a comparison with the course of similar patients prior to the introduction of irradiation therapy.

It is well known that adenoid tissue commonly recurs following

adenoidectomy and necessitates repeated surgical removal in some children; also that severe hearing impairment in children seldom regresses spontaneously. Otolaryngologists and pediatricians know that many children continue to have repeated upper respiratory infections or ear infections in spite of surgical removal of tonsils and adenoids. Irradiation therapy changes the clinical picture after operation for most of these children.

One of the authors (Dr. Polvogt) recently reviewed 835 of his private patients who received irradiation therapy, often combined with operation, sulfonamides or antibiotics, and who have been followed for at least 2½ years, many for 10 to 15 years. He found that:

Of 128 patients treated because of frequent severe colds 40 per cent showed marked improvement.

Of 110 patients suffering from postnasal discharge due to nasopharyngeal infection, excluding Thornwald's disease, 25 per cent had complete relief from this symptom and 75 per cent were improved.

Of 282 patients suffering from impaired hearing thought to be attributable to obstructed eustachian tubes, 85 per cent had a great and lasting improvement in hearing.

Of 122 patients suffering from a variety of complaints thought to be attributable to a focus of infection in the nasopharynx and in whom no other focus could be found, 90 per cent were improved.

Of 87 patients suffering from partial nasal obstruction due to adenoid tissue, 90 per cent were completely relieved and the other 10 per cent were improved. (When there is a large amount of adenoid tssue, irradiation always should be preceded by surgery. There is no point in using large doses of irradiation to treat masses of adenoids when surgery will eliminate most of the tissue. Irradiation should be reserved for treatment of small nodules of lymphoid tissue inaccessible to surgery.)

Of 97 patients complaining of tinnitus, only 3 had relief from this symptom; and of 9 patients complaining only of fullness in the ears, 8 of the group were relieved.

Although well over a thousand applicators are now in use in this country, to our knowledge not a single physician using them has reported unsatisfactory results.

The reader will obtain a cross section of opinion of various physicians who have used this mode of therapy by referring to the clinical reports listed in the bibliography (6–10).

PREVENTION OF DEAFNESS IN CHILDREN

During the last five years, an extensive trial of irradiation therapy has been made in connection with Public Health Clinics for the Prevention of Deafness in Children (especially the Washington County Clinic at Hagerstown, Maryland) (12–14). The clinic organization is as follows:

The clinic is organized as an ear, nose and throat consultation clinic under the auspices of the Department of Public Health. One full-day session every two weeks is sufficient to handle the problems of a population of approximately 75,000 people. An orientation period prior to

SCREENING OF 3rd AND 6th GRADES
WASHINGTON COUNTY, MARYLAND

SCHOOL YEAR	CHILDREN SCREENED	DEGREE OF HEARING IMPAIRMENT					(%) TOTAL IMPAIRED
		SEVERE	MODERATELY SEVERE	MODERATE	SLIGHT	HIGH TONE ONLY	
1944–1945	1616	25	44	24	57	22	10.5
1945–1946	3118	10	8	32	45	17	3.6
1946–1947	2881	10	19	19	47	7	2.5
TOTAL	7615	45	71	75	119	46	3.4

FIG. 7. Data on screening program Washington County, Maryland

the opening of the clinic familiarized the local physicians, school personnel and general population with the aims of the clinic. Patients in need of treatment are discovered by testing the hearing once a year of every child in the 3rd and 6th grades (Fig. 7), by referrals from private physicians, teachers, and public health nurses, who take into account speech defects and the frequency of ear or upper respiratory infections, as well as direct evidence of impaired hearing. At the clinic, complete hearing and ear, nose and throat examinations are made. Simple local therapy and irradiation of the nasopharynx are carried out at the clinic. When operation, antibiotics or frequent local treatment is necessary in addition to irradiation, patients are referred to local physicians or to the nearest medical teaching center. An essential part

of the program is the follow-up by Public Health nurses. All patients are studied over a number of years. Those with irreversible hearing impairments receive adequate help in speech and hearing rehabilitation and, where indicated, properly fitted hearing aids. As yet, this part of our program is still in a developmental stage.

At the Hagerstown Clinic well over a thousand patients have been seen during the past five years. The results listed below are from a statistical study of the records of 400 of these patients who were treated with radium. From our experience, we feel it is safe to say that such clinics are practical and useful. They provide an opportunity to

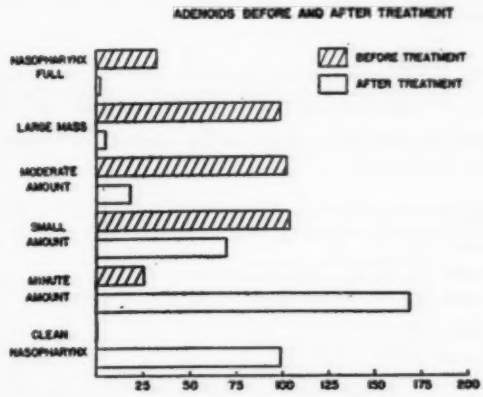

FIG. 8. Chart showing given amounts of adenoid tissue before and after treatment

be of major assistance in the most common serious problems of childhood, i.e., ear and upper respiratory infections and hearing impairment. All communities should institute such programs as soon as adequate physicians, Public Health and clinical facilities are available. One of the major advantages of radium therapy is its simplicity. Not only is the patient ambulatory, but only a few minutes are required for the treatment and there is no discomfort or danger for the patient if the physician uses small doses at the proper intervals. Study of 400 patients treated at the Hagerstown Clinic with radium is analyzed in the accompanying charts (Figs. 8, 9, 10, 11, 12). Patients were treated with radium because of hearing impairment, recurrent respiratory or

ear infections or bronchial asthma. In most instances the last examination was about a year after completion of therapy, but in a few instances treatment has not yet been completed.

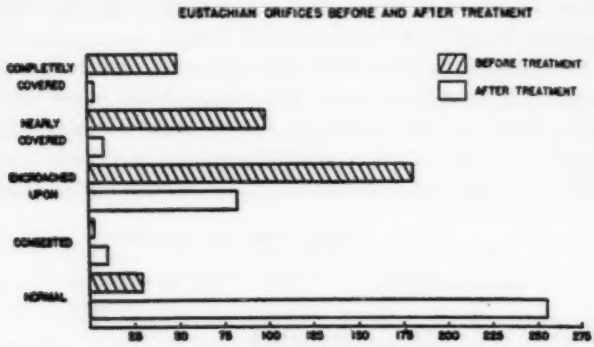

FIG. 9. Chart showing given degree of interference with eustachian orifices before and after treatment.

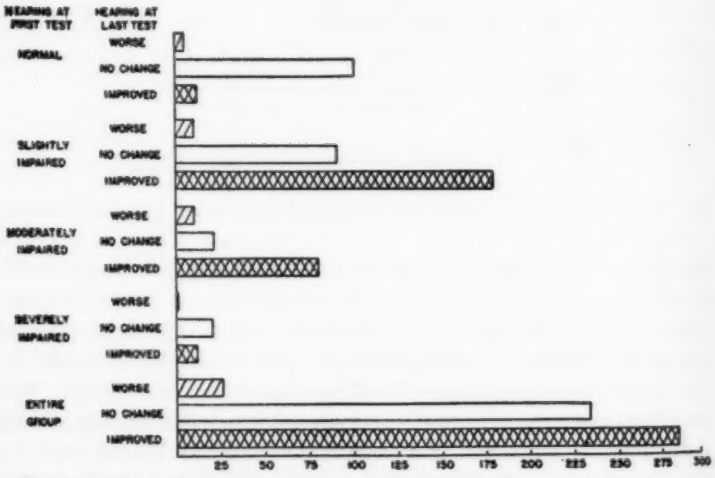

FIG. 10. Chart showing given changes in hearing before and after treatment

The change in the appearance of the adenoids and tubal orifices after radium therapy is clearly shown.

The number of children whose hearing improved following irradiation amounts to nearly half of the group with impaired hearing.

Figure 12 shows the improvement in symptoms following treatment.

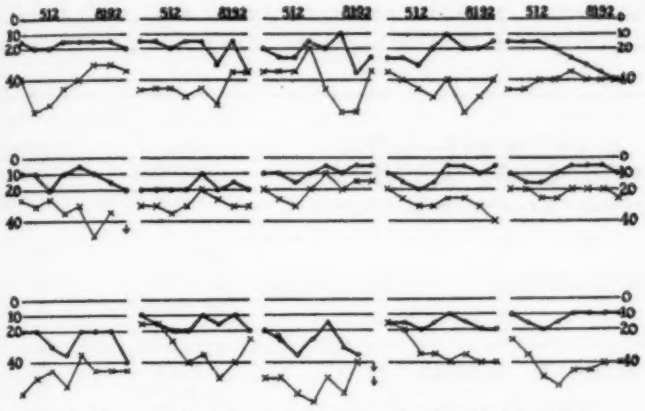

FIG. 11. Audiograms showing improvement in hearing after radium treatment. The lower line of each chart represents hearing before treatment.

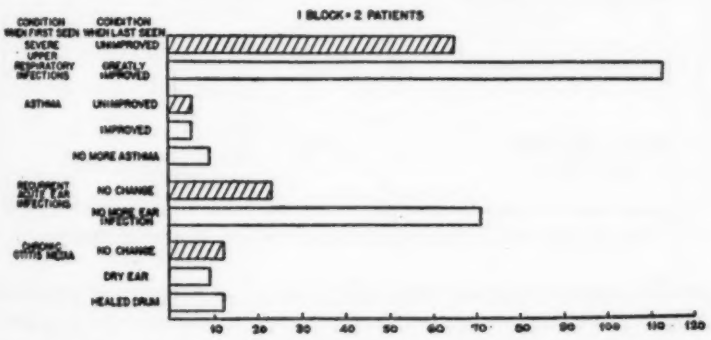

FIG. 12. Patients with infections of the upper respiratory tract, asthma, and infections of the ears who showed given results.

All of these patients were followed through at least one winter after completion of therapy.

Simple local chemotherapy to the nose and ears was also employed in

these patients. Surgical removal of lymphoid tissue was carried out in 71 patients during the period of observation. In 191 patients lymphoid tissue had been removed surgically prior to their first visit to the clinic.

The effect of irradiation on bronchial asthma in children has been difficult to evaluate from the beginning. In an attempt to eradicate all

41 PATIENTS WITH BRONCHIAL ASTHMA (AVERAGE FOLLOW-UP OF 35 MONTHS)			
		WELL	13 (32%)
		BETTER	21 (51%)
		NO BETTER	7 (17%)
MILD ASTHMA	22 (54%)	WELL	9
		BETTER	8
		NO BETTER	5
MODERATE ASTHMA	11 (27%)	WELL	3
		BETTER	6
		NO BETTER	2
MODERATELY SEVERE ASTHMA	1 (2%)	WELL	0
		BETTER	1
		NO BETTER	0
SEVERE ASTHMA	6 (15%)	WELL	1
		BETTER	5
		NO BETTER	0
VERY SEVERE ASTHMA	1 (2%)	WELL	0
		BETTER	1
		NO BETTER	0

FIG. 13. Changes in asthmatic patients following irradiation therapy

possible upper respiratory tract infections in the presence of bronchial asthma, thought to be on an infectious basis, irradiation was first tried on an asthmatic about six years ago. The dramatic improvement in this child, and in several of the others treated since that time, led to a feeling that there might be a basic relationship between infected adenoid tissue and certain types of bronchial asthma. Careful consideration of other factors has forced us to conclude that in asthma, as in the other conditions described above, irradiation of the nasopharynx

IMPAIRMENT THOUGHT TO BE ATTRIBUTABLE TO:	NO. PATIENTS	% OF TOTAL
UPPER RESPIRATORY AND EAR INFECTIONS	551	83
UNKNOWN	64	10
CONGENITAL	15	2
NERVE DEGENERATION	14	2
STENOSIS EXTERNAL EAR	7	1.
MENINGITIS, ETC.	6	0.9
OTOSCLEROSIS	4	0.6
TRAUMA	2	0.5

FIG. 14. Chart showing estimated etiology of hearing impairments (patients seen in Washington County Clinic).

APPROXIMATE LEVEL IN BEST EAR, PURE TONE AUDIOMETRY	% OF TOTAL PATIENTS	
	FIRST AUDIO.	WHEN LAST SEEN
0-20 DECIBEL LOSS	28.6	63.0
25-30	48.9	20.3
35-50	17.1	6.5
55 OR MORE	3.4	3.5
TOTAL LOSS	0.7	0.7
LOSS ONLY ON 8192 OR ABOVE	1.3	6.0

FIG. 15. Hearing of patients seen at the Washington County Clinic at initial test and when last seen (best ear).

must be considered as an auxiliary, even though a uniquely helpful auxiliary, to other forms of treatment. Infected adenoid tissue is an important factor in bronchial asthma, when on an infectious basis, but all other contributory causes must be given due consideration and care.

Of 41 children with bronchial asthma (Fig. 13) treated with irradiation of the nasopharynx, the average follow-up was 35 months (nearly 3 years). In most of these patients desensitization therapy and other standard measures had been tried, but in the majority of these children no improvement had occurred prior to the institution of irradiation therapy.

22 had only mild asthma, 11 had moderate asthma, 1 patient had moderately severe asthma.

Of the entire group, 13 or 32 per cent were well when last seen.

21 or 51 per cent were definitely improved.

7 or 17 per cent had shown no improvement.

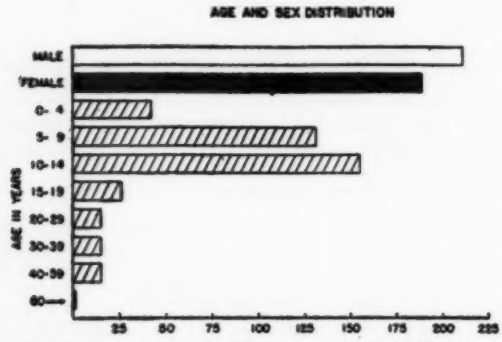

FIG. 16. Sex and age distribution of patients seen at the Washington County Clinic

It is interesting to note that more than 83 per cent of all patients seen in this clinic because of hearing impairment had otitis or upper respiratory infections thought to account for the hearing impairment (Fig. 14). At the last statistical analysis of this group, carried out during 1947, a comparison was made between the hearing in the better ear at the first examination and the hearing in the better ear when the patient was last seen (Fig. 15). Only 28.6 per cent had normal hearing when first seen, but 63 per cent of these children had normal hearing at the last examination. Most of these patients had completed therapy a year or more prior to the survey, but a few are still under treatment. Before treatment was begun, 66 per cent of these patients had a hearing impairment ranging from a 20 to 50 decibel loss; at the last examina-

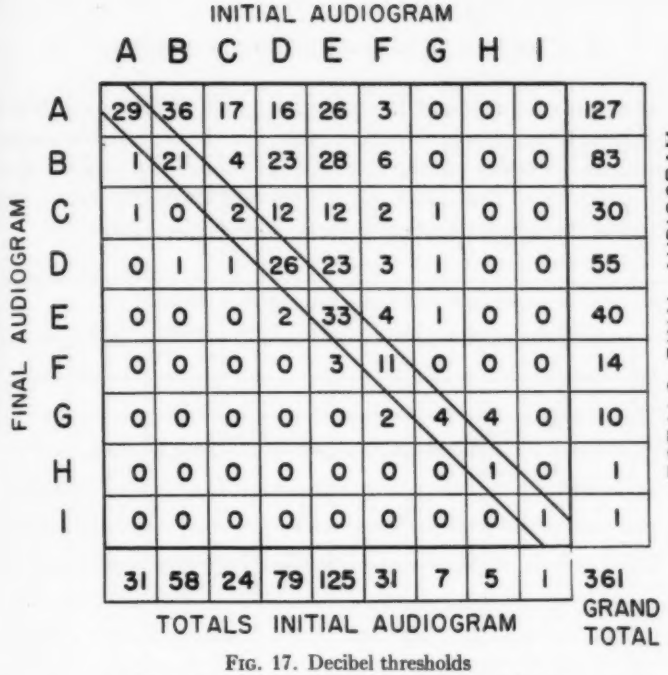

FIG. 17. Decibel thresholds

	one ear	*other ear*
A	All tones better than 25	All tones better than 25
B	No three poorer than 20, none poorer than 30, exception 8192 or above.	No three poorer than 20, none poorer than 30, exception 8192 or above.
C	No five poorer than 20, none poorer than 30, exception 8192 or above.	No five poorer than 20, none poorer than 30.
D	At least five or more poorer than 20 or one or two poorer than 30, from here up to total or almost total loss.	No three poorer than 20, none poorer than 30, exception 8192 or above.
E	At least five poorer than 20 or one or two poorer than 30, from here on up to total or almost total loss.	At least three poorer than 20, maybe one or two poorer than 50, no five poorer than 30.
F	At least five poorer than 30, maybe total or almost total loss.	Five or more poorer than 30, maybe one or two poorer than 50.
G	At least three poorer than 50, maybe total or almost total loss.	Three or four poorer than 50.
H	Five or more poorer than 50 up to	Five or more poorer than 50.
I	Total or nearly total loss.	Total or nearly total loss.

An attempt to show changes in hearing following therapy considering both ears. Groups defined roughly as above. Diagonal strip contains patients who underwent no significant change. Those to right of diagonal improved and those to left became worse.

tion, after the completion of the treatments, only a little over 26 per cent of the patients remained in this group. In the very severe hearing impairments, such was not the case; 3.4 per cent of the patients were in this group when first seen, and 3.5 per cent when last seen. The charts show the age distribution of these patients (Fig. 16).

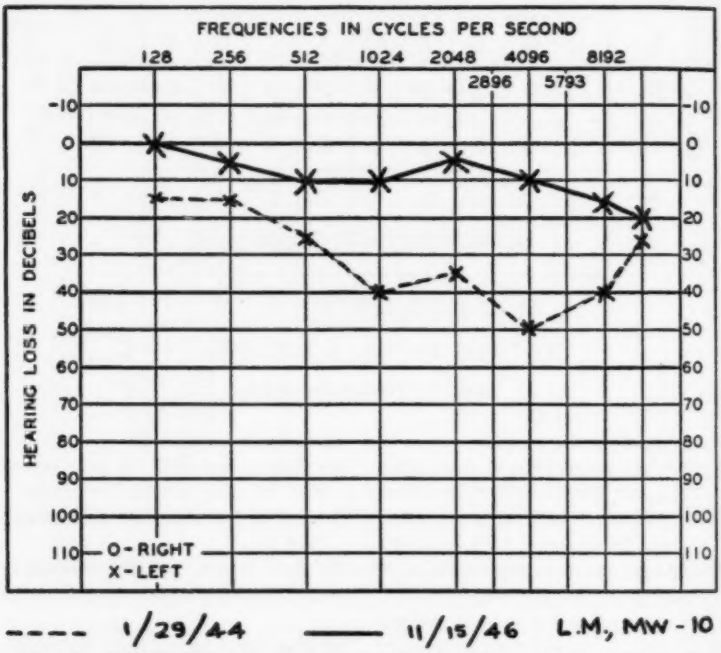

FIG. 18. L. M., MW—10. First seen with acute otitis media, lt. Later given two irradiations of the nasopharynx—total of .66 gm. minutes. Last seen 8/8/47.

A breakdown of 361 patients, taking into consideration the hearing in both ears, shows that only 11 patients had any increase in their hearing impairment (Fig. 17).

In contrast with this, 26 patients, who at the original examination were classified as moderately severe to very severe impairment in one ear and at least moderate impairment in the other ear, had perfectly normal hearing in both ears at the last examination, after the course

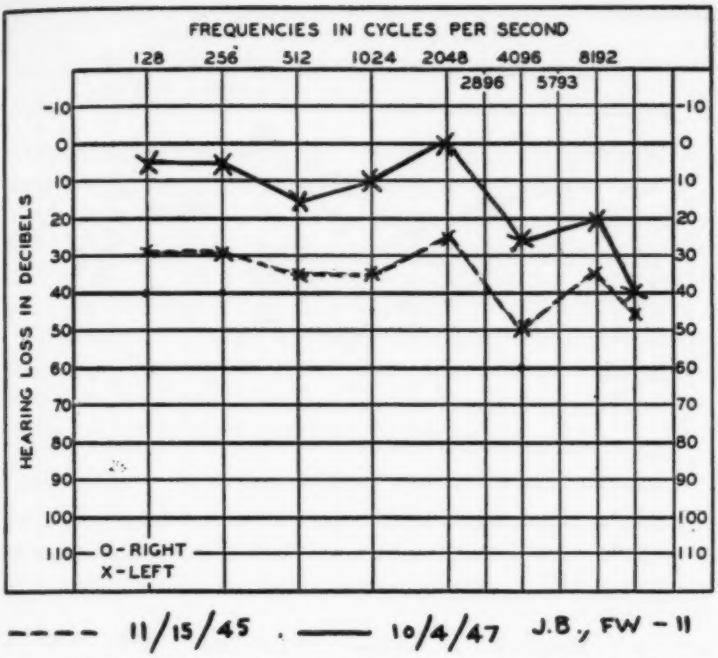

FIG. 19. J. B., FW—11. Chronic otitis media, lt. Six irradiations of the nasopharynx—total of 2.54 gm. minutes. When last seen, 1/24/48, dry ear.

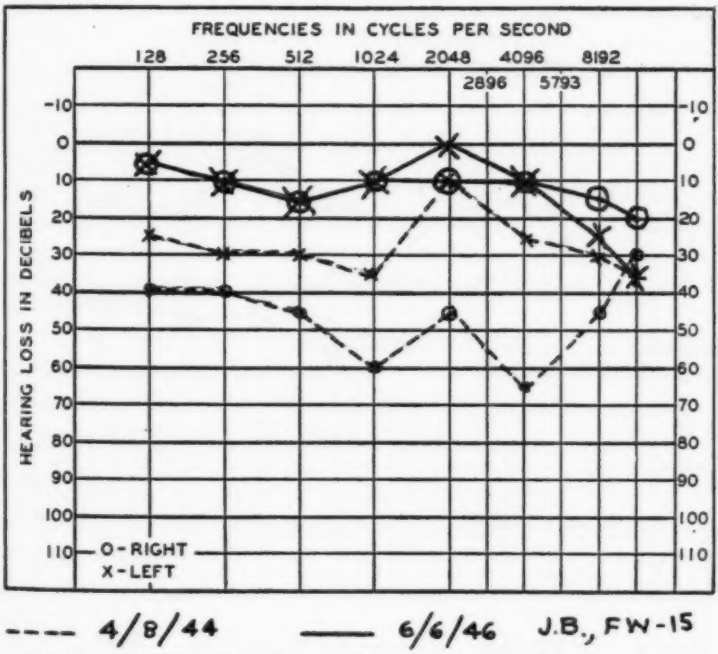

FIG. 20. J. B., FW—15. Two irradiations of the nasopharynx—total of .66 gm. minutes. Last seen 7/26/47.

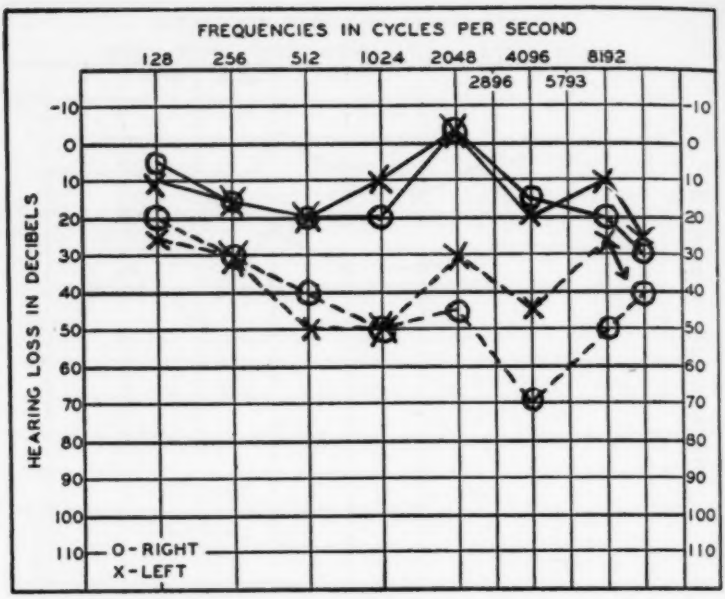

FIG. 21. W. B., MW—15. Chronic otitis media, rt. 5 irradiations of the nasopharynx—total of 1.99 gm. minutes. Ear healed when last seen 11/15/47.

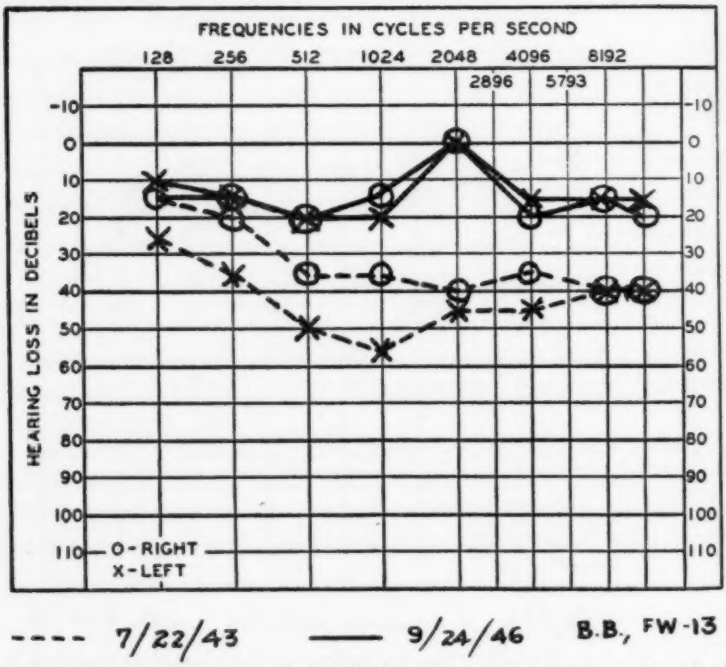

FIG. 22. B. B., FW—13. Six irradiations of the nasopharynx—total of 2.03 gm. minutes. Last seen 9/28/46.

of treatments had been completed. Examination of the accompanying chart will give further data on this analysis.

It is important to note that in this group, as in all of the other groups under our observation, there has never been any complication attributable to the radium treatment. This work covers five years of study and a careful follow up was carried out on nearly every patient.

The changes in hearing are frequently striking enough to excite enthusiasm in both the patient and physician. A few such patients are illustrated in the figures below (Figures 18, 19, 20, 21, 22). These are all children seen and treated in the Hagerstown Clinic.

SUMMARY AND CONCLUSIONS

1. The nasopharynx is the most vulnerable part of the upper respirtory tract. Crypts in nasopharyngeal lymphoid tissue provide the most favorable location for the common cold virus and pathogenic bacteria which cause upper respiratory infections and their complications.

2. The otolaryngologist, by treatments that reduce the size of the lymphoid nodules and the depth of the crypts, can make local conditions unfavorable to recurrent upper respiratory infections.

3. a) In children, surgical removal of adenoids often is followed by recurrence of lymphoid tissue in the nasopharynx and recurrence of undesirable symptoms.

b) Nasopharyngoscopic examination shows that hyperplastic lymphoid nodules are almost invariably present in the lateral walls of the nasopharynx a few months after surgical removal of adenoids in children. Recurrent lymphoid tissue in the nasopharynx should always be sought for and treated in patients with recurring upper respiratory disease, recurring attacks of otitis media, chronic otitis media, recurring attacks of sinusitis, or impaired hearing due to chronic interference with the function of the eustachian tubes.

4. Adenoid tissue is so sensitive to irradiation that doses, so small as to eliminate all possibility of danger, in most instances are sufficient adequately to reduce the size of lymphoid nodules and markedly to decrease their tendency towards hyperplasia.

5. Studies of patients so treated have demonstrated that the following results may be expected in the majority of patients:

a. Improvement in hearing or cessation of progressive impairment

when the symptoms are due to interference with the function of the eustachian tubes.

b. Marked decrease in the number and severity of upper respiratory infections, including acute infections in the sinuses, ears and tonsils.

c. Improvement in many patients, especially children, suffering from bronchial asthma, when the asthma is on an infectious basis and when other forms of therapy such as desensitization are also employed.

6. Irradiation of adenoid tissue has now been used for 24 years and many thousands of patients have been treated. In all this time not a single instance of burn or other complication due to the use of radium has been observed.

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RENAL FUNCTION BEFORE AND AFTER SURGICAL RESECTION OF COARCTATION OF THE AORTA[1]

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Received for Publication May 14, 1948

King in 1926 (1), in his study of four cases of coarctation, confirmed the clinical findings of Wernicke in 1875 and insisted then, and later in 1937 (2), on the presence of arterial pulsations and systolic murmurs in the interscapular region for the diagnosis of coarctation.

In 1928, Abbott (3), in her remarkable statistical study of 200 recorded cases with autopsy, did most to elucidate the clinicopathological picture of coarctation, and expressed the opinion that an elevation of the blood pressure in the arms with a lowered or absent blood pressure in the legs was probably the most important single sign of the presence of the obstruction in the thoracic aorta.

In 1933, Lewis (4) studied nine cases in great detail and insisted on the necessity of taking the femoral pulse, which in those patients is always either absent, or weak and delayed. Bonnet had emphasized this 30 years before (6). He described two important features of the radiological silhouette of the heart: the increased breadth and density of the shadows of the basal vessels which is associated with their dilatation, and the indistinct shadow of the aortic arch in the left oblique position.

More recently, Campbell and Suzman (5) described a new sign elicited by making the patient stoop forward with his arms hanging down vertically. In this position the collateral arteries in the back

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become very prominent and easily visible on ordinary inspection. Campbell and Suzman insisted, as many have done before, on the radiological evidence of notching of the ribs as almost pathognomonic of coarctation.

Since these studies, the diagnosis of coarctation of aorta of the adult type has been made much more frequently during the life of the patients afflicted with this congenital (6) anomaly. The statistical proportion of cases of coarctation of the aorta found at autopsy is approximately 1 per 1500 cases (7), being 4 per 10,000 in Lachte's series, 18 per 22,316 in Fawcett's series, 1 per 4500 in Jaffe and Sternberg's series, 16 per 21,481 in Meixner's series, 4 per 1,000 in Hansteen's series (cited by Blackford (8)), 26 per 19,217 in Evans' series (9).

In recent years, cardiovascular surgery has made tremendous progress due to a better knowledge of the physiology of the body hemodynamics, animal experimentation, and improvement in techniques. Since the pioneer experimental work of Blalock and Park (10), Crafoord (11), Gross (12), Blakemore (13), and since the first successful human case in which the constriction was resected and an end-to-end anastomosis was performed by Crafoord of Sweden in October, 1944, more and more attention and interest have been given to this vascular malformation and more cases have come to surgery for correction and relief.

The purpose of this study was to determine the renal circulatory changes before and after operation and to try to interpret them in the light of new experimental concepts of hypertension (14).

The subjects used for this investigation were the first 17 consecutive patients who came to the Johns Hopkins Hospital for surgical correction of coarctation of the aorta. The diagnosis was established by a careful and detailed examination, x-rays of the chest, direct brachial and femoral artery pressures, and angiocardiograms. Fifteen of these patients were operated upon, and the diagnosis was confirmed at operation.

METHODS

The glomerular filtration rate was determined either by the inulin or by the thiosulfate clearance. It has been shown that both the clearance of inulin and of thiosulfate given in a single injection, or in an

infusion at a constant rate, measure the amount of plasma filtered through the glomeruli (15, 16).

The clearance of para-aminohippuric acid (PAH), or of its acetyl derivative para-aminoacetylhippuric acid (PACA), was used to determine the effective renal plasma flow. Newman has shown in dogs and men that the PACA clearance, after a single injection, remains constant at low plasma concentrations (17).

For patients 1, 2 and 8 a single injection of PACA and thiosulfate was given before and after the operation. Single injections of inulin were given preoperatively to cases 4, 5 and 15. Otherwise, PAH and thiosulfate were given as a priming dose, followed by an infusion maintained at a constant rate of 40 drops/minute. The amount given in the priming dose and in the infusion was the same in the pre- and postoperative studies for the same patient. The dosages were calculated to maintain a blood level of PAH between 1 to 2 mg.% and of thiosulfate between 20 to 30 mg.%.

All the tests were done in the morning, the patient fasting for more than 12 hours and lying in bed. All the patients were catheterized and great care was given to that procedure. Only after the return equalled the amount of distilled water injected in the bladder through the catheter was the test begun. Four or five blood samples and three to five urine specimens of 13 to 20 minutes were taken. At the end of each period the bladder was washed twice with 20 cc. of sterile distilled water and these washings were added to that period.

In each of these experiments, the average of the determinations of the renal filtration rate, the renal blood flow (renal plasma flow $\times \frac{100}{100 - \text{hematocrit}}$) and the filtration fraction were corrected to 1.73 square meter surface area.

SUBJECTS

Of these seventeen patients, twelve were males and five were females. All of them were of the white race. The age of the patients is recorded in Table 2. Twelve were studied pre- and postoperatively. Two died during the operation and one a few days later. Two were not operated upon. Of the twelve cases who underwent surgery, ten had a resection of the constricted segment of the aorta and an end-to-end anastomosis,

TABLE 1

Detailed analysis of the renal function studies and their correlation with the age, and the cuff arm and leg blood pressure in the 17 patients with coarctation of aorta

CASES	AGE	S. A.	BEFORE OPERATION					AFTER OPERATION				
			Cuff B. P.		R.F.R.	R.B.F.	F.F.	Cuff B. P.		R.F.R.	R.B.F.	F.F.
			Arms	Legs				Arms	Legs			
Males												
1. W. B., 442140	23	1.9	200/120	0	116	960	0.231	180/88	140/ 90	148	1050	0.245
2. C. O. C., 442408	13	1.35	170/ 80	0	141	846	0.278					
3. W. D., 424479	18	1.58	185/ 90	0	128	1000	0.236	140/80	130/ 90	112	1050	0.164
4. C. D., 384376	27	1.92	180/ 80	0	100	940	0.203	208/90	140/110	154	1270	0.232
5. W. R. H., 381615	24	1.80	170/100	0	99	785	0.280	130/70	154/100	103	1220	0.167
6. W. H., 430560	20	1.72	180/115	0	103	1070	0.164	125/85	140/ 87	152	925	0.279
7. F. K., 441146	18	2.17	159/ 85	0	133	885	0.272					
8. D. P., 441762	11	1.41	125/ 85	0	139	1140	0.210	122/84	108/ 84	139	1060	0.216
9. C. S., 436928	10	1.10	135/ 85	0	85	1310	0.095	120/90	120/ 90	137	2100	0.114
10. J. W., HLH 55559	7	0.82	140/ 90	?110	138	513	0.438					
11. A. W., 422617	24	1.98	165/ 90	?140	138	717	0.37	155/85	132/ 96	126	1080	0.195
12. E. L. W., 422084	12	1.40	150/ 80	0	160	1170	0.25	135/95	150/100	154	1245	0.213
Average.....					122	945	0.252			138	1220	0.201
Females												
13. B. C., 425369	20	1.63	150/100	0	111	920	0.215	130/75	88/ 70	171	1130	0.269
14. A. H., 388545	34	1.49	220/180	0	122	950	0.240					
15. D. H., 383369	22	1.55	220/110	0	98	550	0.300					
16. M. O., 422966	12	1.40	130/ 85	0	192	1120	0.305	105/65	120/ 80	167	1380	0.216
17. H. S., 440658	14	1.76	195/100	0	139	806	0.326	115/80	125/ 85	146	1020	0.208
Average.....					132	869	0.277			161	1176	0.228

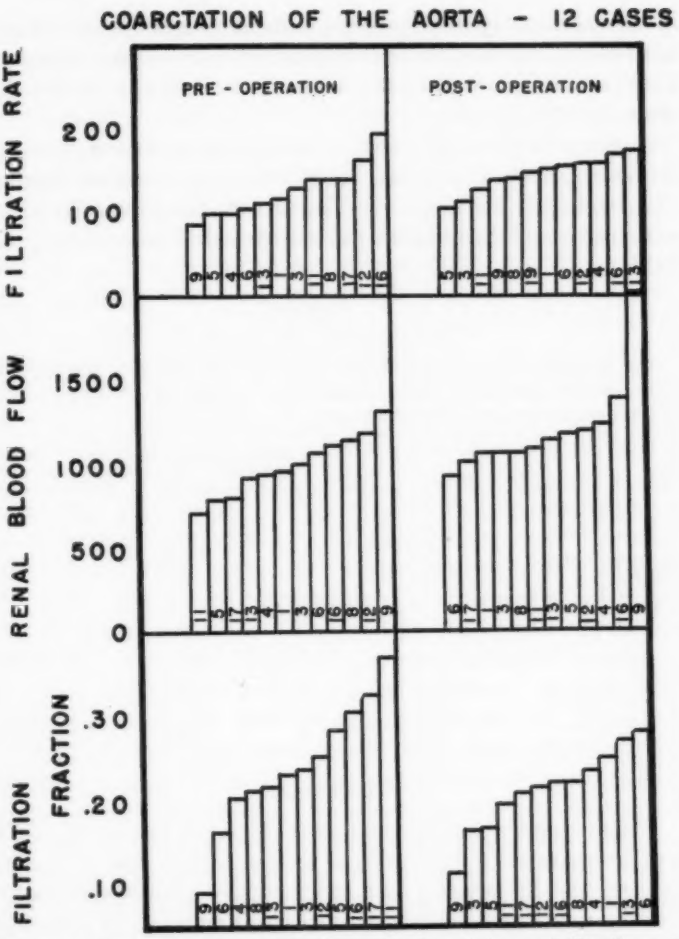

FIGURE 1. Pre- and post-operative determination of the renal filtration rate, the renal blood flow and the filtration fraction in the 12 operated cases.

two (No. 4 and No. 13) had an anastomosis of the left subclavian artery to the distal aorta.

RESULTS

Table 1 and Figure 1 show the results of the renal filtration rate (RFR), the filtration fraction (FF), the renal blood flow (RBF), and

of the auscultatory blood pressure in the arms and the legs before and after the operation in the twelve cases successfully operated upon and in the remaining five who either were not operated upon or died during the surgical procedure.

A change in the renal filtration rate, the renal plasma flow and the filtration fraction of less than $\pm 10\%$ was not considered significant. Postoperatively, the renal blood flow and the glomerular filtration rate were higher and the filtration fraction tended to decrease as shown in Table 2.

TABLE 2

Changes after Operation: 12 Cases

This table shows the changes in the filtration rate, the renal blood flow, the filtration fraction and the arm and leg blood pressure after the operation. A change of less than 10% was not considered of any significance.

	INCREASE MORE THAN 10%	DECREASE MORE THAN 10 %	NO CHANGE LESS THAN 10%
R. Filtration Rate	5	2	5
R. Blood Flow	7	1	4
Filtration Fraction	4	6	2
Cuff B.P.:			
Arms:			
S.	1	8	3
D	2	7	3
Legs			
S.	12		
D.	12		

DISCUSSION

The preoperative findings confirm those of Friedman et al. (18) who first demonstrated a diminution of the renal blood flow in all of their six cases and the presence of a compensatory efferent arteriolar constriction resulting in a nearly normal filtration rate. It is essentially the same pattern as shown by Goldring and Chasis (19) in essential hypertension. The postoperative results also show that in the majority of patients the surgical procedure increases the renal blood flow and relieves the constriction of the efferent artery. Thus the filtration fraction falls.

After operation, one patient (case 6) showed a decreased renal blood

flow and four patients (cases 1, 3, 8 and 13) showed an insignificant change (less than 10%). It is possible that this might be due to the fact that these patients were young (between 10 and 25 years of age) and that anxiety, their considerable apprehension of the catheterization, and their fear of the repeated venipunctures would have been sufficient to bring a decrease in the renal blood flow. Smith has shown in his *Lectures on the Kidney* a beautiful example of this situation (20) in which a hypertensive patient became alarmed in the course of the experiment and his renal blood flow dropped 50%.

It is impossible, even by the careful analysis of our data, to draw a definite conclusion on the nature of the hypertension in most of the cases of coarctation (adult type) of the aorta. Depending probably on the age at which they are seen, these cases can be divided on the basis of the clinical studies of King, Blackford, Abbott and others into three groups: the normotensive group, the systolic hypertensive group, and the systolic-diastolic hypertensive group. The first one does not raise any problem. The systolic hypertension in the second group, (the diastolic pressure being within normal limits) is evidently due to the mechanical obstruction of the constriction of the aorta and to the inability of the large arteries proximal to the coarctation to dilate any further to accommodate the quantity of blood ejected from the left ventricle at each systole. In those cases, normal diastolic pressure indicates that the peripheral resistance is not increased. In many cases of coarctation the cardiac index is within normal limits (21, 22), so that the systolic pressure in the large arteries of the upper extremities will be elevated because of the considerable diminution of the immediate vascular area in which the blood is ejected from the left ventricle and the inability of the large arteries of the upper extremities to distend any further. Bell (25) states that this situation is in some respect similar to aortic stenosis where the obstruction produces left ventricular hypertrophy and intra-ventricular hypertension. Another factor may also play a part, as illustrated in the Figure 2 showing the follow-up of the arm blood pressure in one patient before and after operation. This patient, because of the presence of severe arteriosclerosis with calcareous deposits in the aorta, had an anastomosis of the left subclavian artery to distal aorta as had been done successfully in experimental animals by Blalock and Park (10). Despite a marked increase

in renal blood flow after operation, he presented a further elevation in systolic pressure three and a half months later.

The hypertension in the systolic-diastolic group (the largest group), in which the arm diastolic and the systolic pressure is above normal, seems to result from a combination of the factors described above with a humoral mechanism. It is possible that a relative renal ischemia or a diminished pulse pressure in the kidneys would produce a situation analogous to the hypertension produced by the Goldblatt kidney.

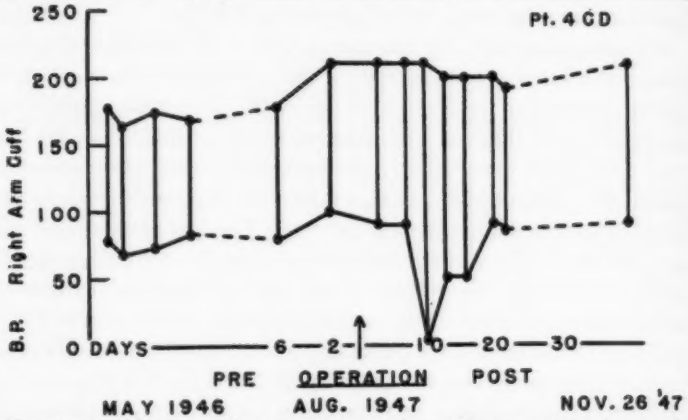

FIGURE 2. This is a follow-up of the cuff arm blood pressure in a patient (C.D.) who, because of severe arteriosclerosis of the aorta, had an anastomosis of the left subclavian artery with the aorta distally to the constriction.

There is much indirect evidence to show the peripheral resistance in such patients is increased and that this increase is generalized. It has been shown by Steele (29) that the femoral mean pressure obtained by the direct method is frequently elevated. Graybiel et al. (25) could not find any change in the vessels themselves in studying the arterioles of the muscles and the skin from the arm and the leg from five cases of coarctation. The experimental work done on rats by Rytand (26) and on dogs by Page (27), Brotchner (28), Steele (29) and Goldblatt (30) seems to indicate that, in animals, the hypertension produced in the upper and lower extremities by constricting the aorta above the renal arteries is of renal origin.

The present study shows that, in most cases, there is a relationship between the renal blood flow and the blood pressure, but the nature of

this relationship cannot be determined. At any rate, the renal circulatory changes and the hypertension are completely reversible.

CONCLUSION

Seventeen consecutive patients with coarctation of the aorta of the adult type were studied for their renal filtration rate and blood flow. Twleve of these were also studied postoperatively.

The surgical resection of the constricted segment and the end-to-end anastomosis of the aorta resulted in most of the patients in an increase of their renal blood flow and a decrease in the filtration fraction.

The blood pressure and the renal ischemia in coarctation of the aorta can be completely normal after relief of the aortic constriction.

We are deeply indebted to Dr. Alfred Blalock and the Department of Surgery for the opportunity to study these patients and use their records.

Other hemodynamic studies in these patients will be reported in the Annals of Surgery, by Blalock, Bing and their co-workers.

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PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE

VI. Adaptations to Anoxia in Congenital Heart Disease with Cyanosis[1]

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Received for Publication May 17, 1948

Patients with the cyanotic type of congenital heart disease and individuals at high altitude show physiological changes attributable to a deficiency of pressure at which oxygen is transferred from capillary blood to the tissues. Barcroft has advanced the concept that acclimatization to high altitude consists of a series of adaptations which tend to alleviate this deficiency by attempting to restore tissue oxygen pressure toward normal sea level values. This, he suggests, is mainly accomplished by increased pulmonary ventilation, polycythemia, and a shift of the oxygen dissociation curve to the left (1).

In recent studies performed on normal adults in the low pressure chamber, Houston and Riley found that their subjects were likewise able to raise the oxygen pressure of the tissues toward normal sea level values. This was accomplished by reducing the difference between the oxygen pressure of inspired air and mean capillary blood. Increased pulmonary ventilation and the shape of the oxyhemoglobin dissociation curve were the principal factors in accomplishing this. Additional, but less important, mechanisms were cardiac output and the oxygen carrying capacity of the blood (2).

Physiological studies undertaken on patients with the cyanotic type of congenital heart disease have shown that in this condition the oxygen saturation of peripheral arterial blood is reduced from birth. At high altitude the lowering of the oxygen saturation in peripheral arterial blood is the result of decreased partial pressure of oxygen in the inspired

[1] This work was supported by grants from the Commonwealth Fund and the Carolyn Rose Strauss Foundation.

air. On the other hand, the cause of anoxemia in congenital heart disease is a reduction in the effective pulmonary blood flow (3). Regardless of the initiating factor, the oxygen saturation and the partial pressure of oxygen of arterial blood are decreased in normal individuals living at reduced barometric pressure and in patients with congenital heart disease and cyanosis. Thus, the adaptive processes in both conditions must be directed toward the same goal, the restoration of the tissue oxygen pressure to normal. The present investigation consists in a study of these processes in patients with the cyanotic types of congenital heart disease. The results of these studies will be compared with those obtained in individuals exposed to decreased barometric pressure.

METHODS

Tests were performed on a total of 35 patients with tetralogy of Fallot, studied for diagnostic purposes. Reports on the hemodynamics of these individuals have been published in preceding papers (3). The methods and calculations pertaining to the present study will be described in the following paragraphs.

The minute volume of ventilation was determined by measuring the quantity of expired air collected in a Douglas bag over periods ranging from 1½ to 3 minutes. The oxygen consumed and carbon dioxide produced were determined from analysis of this expired air. All values were corrected to dry volume at standard pressure and temperature (STPD). The basal metabolic rate was calculated from the oxygen consumption using the diagram of du Bois (4). Alveolar air was calculated according to a method previously described (5). The blood pH was determined with a Leeds and Northrup shielded glass electrode installed in an incubator regulated to a temperature of 38°C. In the presence of a decrease in pCO_2 the carbon dioxide content of serum is predominantly in the form of bicarbonate. Therefore, the total carbon dioxide content of serum rather than the serum bicarbonate was determined. The partial pressure of carbon dioxide in plasma was then calculated from the Henderson-Hasselbach equation, using the line chart of Peters and Van Slyke (6). The presence of an intracardiac shunt precluded the calculation of effective alveolar gas pressures (7). Consequently, alveolar pO_2 was calculated from the respiratory quo-

tient, the carbon dioxide content of alveolar air and the oxygen content of alveolar and inspired air, using Barcroft's formula (8).

In order to study the oxygen transfer from inspired air to tissue capillaries, it was necessary to determine the partial pressure of oxygen in arterial and in mixed venous blood. This can be accomplished by measuring the pO_2 of the blood directly (9) or by determining it from the oxygen saturation of the blood and the dissociation curve of oxygen. The latter procedure was adopted since in anoxemic individuals the values for both arterial and mixed venous blood saturations lie on the steeper part of the dissociation curve. On this portion of the curve the pO_2 can be determined from the oxygen saturation with a much greater degree of accuracy than at the flat upper region. However, the use of the oxygen dissociation curve for the determination of tensions precluded accurate determination of the tensions of oxygen in pulmonary vein blood. The saturation in that vessel had been found to be above 95 per cent. At this high oxygen saturation the pO_2 cannot be accurately determined from the curve. The dissociation curve of individuals with tetralogy of Fallot was obtained by the "in vivo" method of Riley and associates (10). Forty samples were collected from the arterial and venous blood of 35 cyanotic individuals (Fig. 1).

In a study of gradients of oxygen pressure from inspired air to capillary blood, the determination of the oxygen pressure in the latter is of particular significance. Since the capillary pressure cannot be determined directly and varies with anatomical location of the capillary, calculations must be indirect. Barcroft's formula was used:

Mean capillary pO_2

$$= \text{mixed venous } pO_2 + \frac{(\text{arterial } pO_2 - \text{mixed venous } pO_2)}{3} \quad (11).$$

The value thus obtained represents, according to Houston and Riley, "the oxygen pressure, which, if it prevailed throughout the entire length of all the capillaries of the body, would not alter the quantity of oxygen diffusing under actual physiological conditions." The normal value for arterial pO_2 was assumed to be 88 mm. Hg (saturation 96 per cent), that of mixed venous blood 39 mm. (saturation 74 per cent). From these values a normal arteriovenous difference of 49 mm. (22 per cent oxygen saturation) and a mean capillary pressure of 55

mm. was calculated. Consequently the normal gradient in oxygen pressure from arterial to mean capillary blood equalled 33 mm.

Following Barcroft's example, the transfer of oxygen from inspired air to the tissue capillaries was divided into various gradients. In normal individuals gradients exist between the oxygen tension of inspired air and alveolar air (Barcroft's gradient I), between the oxygen tension of alveolar air and arterial blood (Barcroft's gradient II), and finally

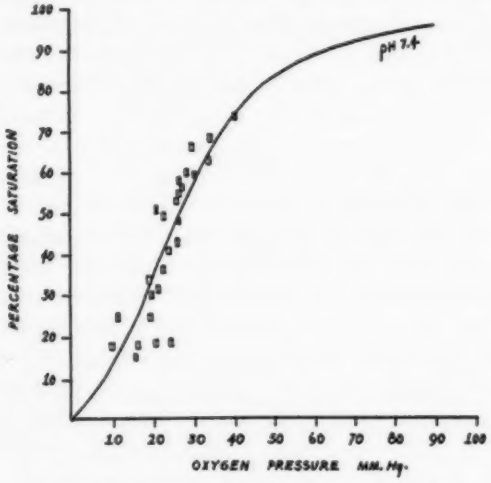

FIG. 1. Grouping of arterial oxygen pressures about a standard dissociation curve.

between the oxygen tension of arterial and mean capillary blood (Barcroft's gradient III). In patients with tetralogy of Fallot, however, the presence of an intracardiac right to left shunt introduces an additional gradient between the pO_2 of alveolar air (or, more accurately, the pO_2 of pulmonary vein blood) and of peripheral arterial blood. For reasons outlined above, however, the partial pressure of oxygen in pulmonary vein blood could not be determined with accuracy. Therefore, only the gradient from alveolar air to peripheral arterial blood was calculated.

In evaluating the factors which determine the pO_2 gradient between arterial and mean capillary blood (gradient III) it is necessary to compare this gradient as it exists in the normal at sea level with gradient III in patients of this series. The difference between gradient III in the normal and gradient III in the individuals of this series represents the total gain in this gradient for these patients. This total gain is achieved through the properties of hemoglobin, the oxygen carrying capacity of the blood, and changes in systemic blood flow. In order to determine the relative contribution of each of these factors certain calculations are necessary.

A. *The effect of the dissociation curve:* The normal arteriovenous difference in oxygen saturation (22 per cent) was subtracted from the arterial oxygen saturation of each individual patient. A venous saturation was thus computed. The partial pressure of oxygen for the observed arterial saturation and for the calculated venous saturation was then determined by reference to a standard oxygen dissociation curve. From these two values the mean capillary pO_2 was calculated. The gradient between arterial pO_2 and the calculated mean capillary pO_2 was then obtained by subtraction. To obtain the gain in gradient III through the dissociation curve alone, the calculated gradient III was subtracted from the normal gradient III.

B. *The effect of hemoglobin:* The per cent hemoglobin of each individual patient was calculated according to the formula: per cent observed Hgb. $= \frac{\text{observed oxygen capacity vol. per cent}}{\text{normal oxygen capacity (20 vol. per cent)}} \times 100$. The arteriovenous oxygen difference for the percentage of observed Hgb. was then determined according to Barcroft's formula (11): arteriovenous oxygen difference per cent observed Hg $=$

$$\frac{\text{normal arteriovenous oxygen difference (22 per cent)} \times 100}{\text{percentage observed hemoglobin}}$$

This calculated arteriovenous difference in saturation was subtracted from the arterial oxygen saturation of each individual patient. It was then possible to obtain the pO_2 of mixed venous blood, the mean capillary pressure of oxygen, and gradient III, all with reference to the effect of hemoglobin. The gain due to increased hemoglobin was then determined according to the equation: Gain through hemoglobin $=$ gradient III in the normal $-$ (gradient III calculated for Hgb. $+$ gain through curve).

C. *The effect of the systemic blood flow:* The effect on gradient III resulting from changes in the systemic blood flow was calculated according to the formula: Effect of systemic blood flow = total gain — (gain through dissociation curve + gain through hemoglobin). Methods involved in the calculation of the systemic flow have been described in detail in a preceding publication (12).

General technique: All blood oxygen and carbon dioxide contents were determined by the manometric method of Van Slyke and Neill (13). The oxygen capacity of blood was obtained by equilibration of 8 cc. of blood with room air in tonometers of 350 cc. capacity. The blood was collected in syringes under oil and transferred under oil into bottles of 20 cc. capacity containing 2 mgs. sodium fluoride and 15 mgs. potassium oxalate. The oxygen tension was determined by the method of Riley et al. (9). All gas analyses were performed in the Haldane apparatus.

Results and discussion: The oxygen dissociation curve of hemoglobin. Figure 1 demonstrates that the partial pressure of oxygen obtained on a series of 16 patients with tetralogy of Fallot cluster around the standard oxygen dissociation curve of hemoglobin. As the pH of these samples was close to 7.4, the points determined on the curve express the true relationship between the partial pressure of oxygen and the oxygen saturation. The use of a standard oxygen dissociation curve is therefore valid. This observation is at variance with the findings of Barcroft on subjects at high altitude. He found a shift of the oxygen dissociation curve to the left in natives living high in the Andes (11). On the other hand, Houston and Riley (2), as well as Keys (14), noticed a shift of the oxygen dissociation curve to the right in individuals exposed to low oxygen pressures.

Pulmonary ventilation and respiratory gas exchange. Table I presents the results in the determination of the minute volume of respiration, the oxygen uptake, and the carbon dioxide output. In 29 out of 30 patients the minute volume of respiration was increased above normal. In the absence of an intracardiac shunt an increase in respiratory minute volume lessens the gradient between the oxygen tension of inspired air and capillary blood by reducing the difference between alveolar and arterial pO_2. In individuals with tetralogy of Fallot, on the other

hand, the effect of hyperventilation is largely offset by the presence of the right to left intracardiac shunt (Fig. 3).

TABLE I

NAME	SURFACE AREA M^2	LV/MIN./ M^{2*}	R.Q.	CC/MIN. O_2 CONS.	CC/MIN. CO_2 OUTPUT	BMR
V. S.	1.68	5.5	.89	241	218	+9
D. M.	0.83	3.6	.87	95	85	−32
D. S.	1.30	3.4	.83	138	117	−18
O. J.	1.80	2.5	.90	162	152	−30
M. C.	1.28	4.1	.88	161	143	−5
L. S.	1.68	3.0	.88	172	153	−23
C. H.	1.43	3.2	1.0	119	119	−34
R. A.	1.46	4.7	1.0	156	157	−25
G. S.	1.50	2.7	1.08	103	113	−48
R. C.	1.35	6.1	1.26	162	207	−24
A. P.	1.30	3.7	.82	131	109	−23
L. P.	1.59	3.3	.81	164	134	−19
J. H.	1.54	5.6	.82	117	147	−27
A. F.	0.66	9.5	.90	126	115	−8
J. O.	1.68	2.4	.73	180	153	−27
V. A.	0.76	6.1	.83	105	91	−26
D. F.	1.34	5.0	1.08	150	165	−33
J. F.*f*	0.95	3.4	.90	77	72	−48
J. F.*m*	1.70	4.7	1.10	211	241	−22
E. R.	1.43	3.5	1.08	112	122	−39
B. H.	0.96	7.3	1.18	111	132	−28
D. B.	0.77	7.5	1.02	95	97	−24
V. B.	1.01	6.3	.87	123	107	−24
R. W.	1.50	7.8	1.18	195	231	−15
R. F.	1.02	7.9	.88	161	142	−1
J.M.*f*	0.82	5.1	.98	91	90	−4
A. S.	1.59	3.9	.89	148	131	−26
A. OC.	0.93	4.5	.83	96	80	−41
S. C.	1.50	4.6	1.03	135	140	−46
E. L.	1.44	5.2	1.01	215	220	+18

* Normal at 0° and prevailing atm. p. = 2.82.

Of special interest is the reduction of the oxygen consumptions and consequently of the basal metabolic rate. In 28 of 30 patients the basal metabolic rate was either markedly reduced or at the lower limit of normal. In one individual (G. S.) in whom one pulmonary artery

was absent, a value of −45 was determined. In two patients of this series (E.L., V. S.) the basal metabolic rate was positive. These findings suggest that metabolic adjustments take place which keep the tissue oxygen tension at the lowest possible level. In contrast, Houston and Riley among others have shown that the oxygen consumption of normal individuals remained the same at high altitude as at sea level. Their observation implies that cellular metabolism remains normal as the barometric pressure decreases (2).

The acid base balance. The findings concerning the hydrogen ion concentration, the serum carbon dioxide, the partial pressure of carbon dioxide, and the serum chloride of 21 patients are illustrated in Figure 2. It may be seen that the pH was within normal range. The values for total carbon dioxide, on the other hand, were significantly reduced. Since the pH varies directly with the bicarbonate and inversely with the pCO_2, the reduction in serum carbon dioxide was accompanied by a decrease in the pCO_2. Serum chloride (Fig. 2) and blood lactic acid values were within normal limits (15). The assumption might be ventured that the failure of the pH to rise as the pCO_2 fell is the result of increased elimination of bicarbonate. These results contrast with those obtained by a series of investigators on normal individuals at high altitude. Keys, for instance, demonstrated increased alkalinity of the blood in persons living at altitudes ranging from 4,000 to 12,000 feet; above this altitude he noticed either no further change or a return to values observed at sea level (16). Dill and associates found that the pH rose as the partial pressure of oxygen in the inspired air decreased (17). Similar results were obtained by Houston and Riley in the low pressure chamber (2).

The oxygen transfer system. Changes in the oxygen transfer system from inspired air to mean capillary blood are illustrated in Figure 3. In the patients of this series the average gradient between the pressure of oxygen in inspired and alveolar air (gradient I) is 25 mm. of Hg. This represents a gain of 32 mm. Hg since in the normal at sea level gradient I equals 57 mm. At altitudes of 20,000 feet the reduction in gradient I is of similar magnitude. This reduction in gradient observed in both conditions is the result of increases in respiratory minute volume.

The average drop in pO_2 from alveolar air to arterial blood (gradient

II) in individuals with congenital heart disease equals 57 mm. Hg (Fig. 3). In the normal individual at sea level this gradient is 5 mm. and at altitudes of 20,000 feet it is 2 mm. (2). The large difference

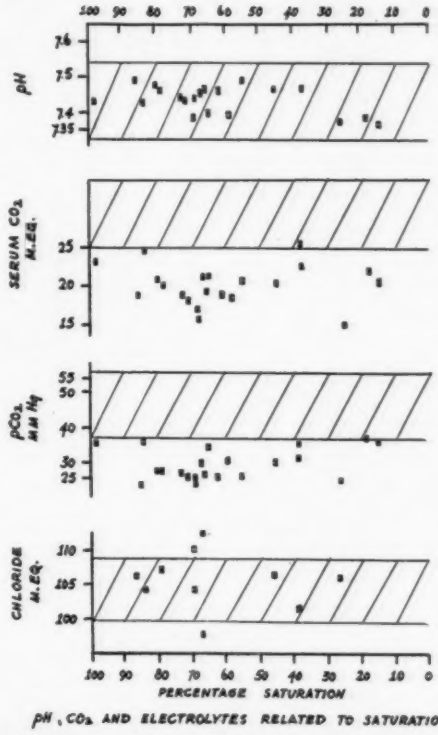

FIG. 2. Relationship of pH, CO_2, electrolytes, and saturation in patients with congenital heart disease. Shaded areas indicate normal range. Serum CO_2 and pCO_2 are decreased proportionately. As a result the pH remains within normal range.

in this gradient between the normal and patients with the cyanotic type of congenital heart disease is the result of the intracardiac right to left shunt in the latter. The shunt lowers the oxygen tension of arterial blood and it is because of this that hyperventilation loses its effect in the patients of this series. Consequently a diminution of the

oxygen gradient between the arterial and mean capillary blood (gradient III) remains the only means of restoring the tissue oxygen tension toward normal.

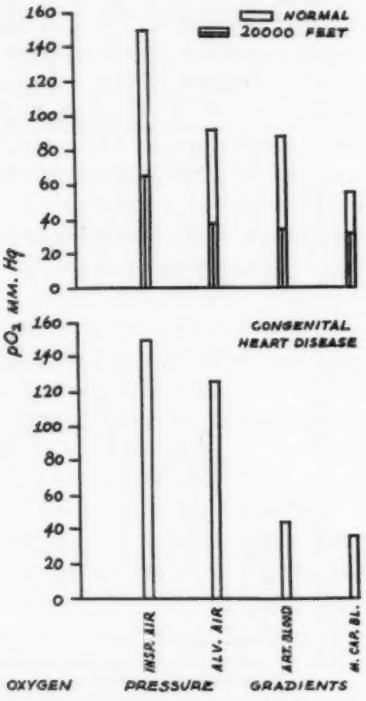

FIG. 3. Gradients in the oxygen transfer system from inspired air to capillary blood in normal individuals at sea level and at high altitude, and in patients with congenital heart disease.

It has been shown that gradient III may be lowered by the integrated action of three major factors. The first of these is the shape of the oxygen dissociation curve of hemoglobin. The shape of this curve is such that on its steeper portion a given drop in saturation produces a much smaller fall in oxygen tension than at its flat upper part. This fact is of major importance in reducing gradient III at high altitude

where the points for arterial oxygen saturation lie on the steep part of the curve.

TABLE II

Effect due to Curve

NO.	NAME	% ART. SAT.	% VENOUS SAT. CALCUL.	OBS. ART. PO_2	CALC. MIXED VENOUS PO_2	ΔPO_2	CALC. MEAN CAP. PO_2	CALC. GRADIENT III	GAIN DUE TO CURVE
1	V. S.	60.6	38.6	32.0	21.5	10.5	25.0	7.0	26.0
2	D. M.	79.8	57.8	45.0	30.0	15.0	35.0	10.0	23.0
3	D. S.	63.8	41.8	33.3	23.0	10.3	26.4	6.9	26.1
4	O. J.	75.0	53.0	40.5	28.0	12.5	32.2	8.3	24.7
5	M. C.	69.0	47.0	36.0	25.0	11.0	28.7	7.3	24.7
6	L. S.	71.5	49.5	38.0	26.2	11.8	30.1	7.9	25.1
7	C. H.	60.8	38.8	31.8	21.8	10.0	25.1	6.7	26.3
8	R. A.	82.0	60.0	47.8	31.1	16.7	36.7	11.1	21.9
9	G. S.	77.7	55.7	42.5	29.6	12.9	33.9	8.6	24.4
10	R. C.	72.2	50.2	38.3	26.5	11.8	30.4	7.9	25.1
11	A. P.	85.5	63.5	53.0	33.0	20.0	39.7	13.3	19.7
12	L. P.	79.0	57.0	44.0	29.8	14.2	34.5	9.5	23.5
13	J. H.	57.4	35.4	30.2	20.0	10.2	23.4	6.8	26.2
14	A. F.	57.8	35.8	30.4	20.2	10.2	23.6	6.8	26.2
15	J. O.	80.0	58.0	45.7	30.2	15.5	35.4	10.3	22.7
16	V. H.	89.0	67.0	60.0	35.0	25.0	43.3	16.7	16.3
17	D. F.	80.1	58.1	45.7	30.2	15.5	35.4	10.3	22.7
18	J. F.*f*	66.0	44.0	34.5	23.9	10.6	27.4	7.1	25.9
19	J. F.*m*	78.6	56.6	43.6	29.5	14.1	34.2	9.4	23.6
20	E. R.	84.5	62.5	51.5	32.6	18.9	38.9	12.6	20.4
21	B. H.	73.4	51.4	39.1	27.1	12.0	31.1	8.0	25.0
22	D. B.	58.6	36.6	30.5	20.5	10.0	23.8	6.7	26.3
23	V. B.	75.0	53.0	41.3	28.0	13.3	32.4	8.9	24.1
24	R. W.	81.0	59.0	46.5	31.0	15.5	36.2	10.3	22.7
25	R. F.	70.9	48.9	37.3	26.0	11.3	29.8	7.5	25.5
26	J. M.*f*	78.0	56.0	42.5	29.1	13.4	33.6	8.9	24.1
27	A. S.	74.8	52.8	41.3	27.9	13.4	32.4	8.9	24.1
28	A. OC.	64.5	42.5	33.5	23.2	10.3	26.6	6.9	26.1
29	S. C.	91.0	69.0	66.0	36.0	30.0	46.0	20.0	13.0
30	E. L.	82.5	60.5	48.5	31.5	17.0	37.2	11.3	21.7

The second factor is the increase in the quantity of hemoglobin. According to Haldane and Priestley (18), polycythemia maintains the oxygen saturation and tension of venous blood at a higher level since less oxygen is discharged from each individual red cell. This raises

the mean capillary pressure of oxygen and leads to reduction in gradient III. However, it has been found that at high altitude the additional gain in gradient III due to polycythemia was insignificant (2).

A rise in cardiac output represents the third factor. Increased blood flow through the tissues reduces the difference in the arteriovenous oxygen saturation and thereby raises the mean capillary pressure of oxygen. Houston and Riley found an increase in cardiac output dur-

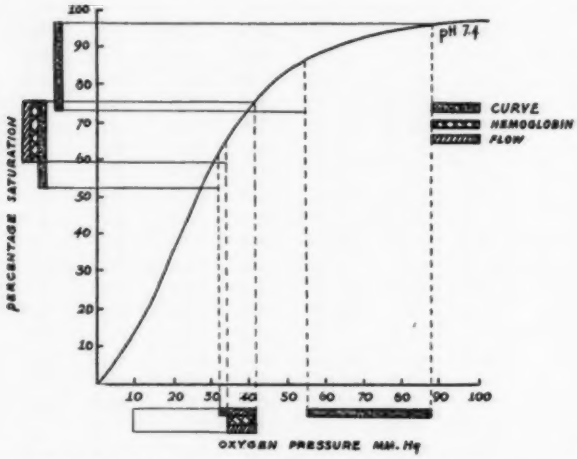

FIG. 4. The role of three factors in decreasing the oxygen pressure gradient from arterial to mean capillary blood. The gain over the normal is represented by the unshaded area in the lower rectangle.

ing the first days of exposure to low barometric pressure (2), and Harrison and Blalock demonstrated that anoxia had a similar effect (19). Most investigators agree, however, that the cardiac output returns to normal during the chronic phase of anoxia (20).

An evaluation of the role played by each of these mechanisms reveals that in the patients of this series the shape of the dissociation curve is the most important factor. Table II indicates that because of the characteristics of the curve alone, the gradient between arterial and mean capillary blood equals 9.4 mm., that is, 23.6 mm. less than in the normal individual at sea level. It can be seen from Figure 4 that this

factor is primarily responsible for the reduction in gradient III. The second factor, the oxygen capacity of blood, is less significant, the aver-

TABLE III

Effect due to Hgb

NO.	NAME	OBS. CAP. VOL. %	HGB GM.	% HGB	A-V DIF. IN % SAT. CALCUL. FOR HGB	% OBS. SAT.	% CALC. MIXED VENOUS SAT.	OBS. ART. pO_2	CALC. MIXED VENOUS pO_2	A-V ΔpO_2	MEAN CAP. pO_2	GRADIENT III REF. TO HGB	GAIN
1	V. S.	34.0	25.5	170.0	12.90	60.6	47.7	32.0	25.7	46.3	27.8	4.2	2.8
2	D. M.	28.5	21.3	142.5	15.40	79.8	64.4	45.0	33.4	11.6	37.3	7.7	2.3
3	D. S.	32.0	23.8	160.0	13.70	63.8	50.1	33.3	26.5	6.8	28.8	4.5	2.4
4	O. J.	32.0	23.8	160.0	13.70	75.0	61.3	40.5	32.0	8.5	34.8	5.7	2.6
5	M. C.	35.3	26.7	176.5	12.40	69.0	56.6	36.0	29.0	7.0	31.3	4.7	2.6
6	L. S.	34.0	25.5	170.0	12.90	71.5	58.6	38.0	30.2	7.8	32.8	5.2	2.7
7	C. H.	26.3	19.6	131.5	16.70	60.8	44.1	31.8	24.0	7.8	26.6	5.2	1.5
8	R. A.	35.2	26.3	176.0	12.50	82.0	69.5	47.8	36.5	11.3	40.3	7.5	3.6
9	G. S.	31.5	23.7	157.5	13.95	77.7	63.75	42.5	33.2	9.3	36.3	6.2	2.4
10	R. C.	31.7	23.7	158.5	13.85	72.2	58.35	38.3	30.3	8.0	33.0	5.3	2.6
11	A. P.	21.0	15.7	105.0	20.90	85.5	64.6	53.0	41.5	11.5	45.3	7.7	5.6
12	L. P.	30.3	22.7	151.5	14.50	79.0	64.5	44.0	33.5	10.5	37.0	7.0	2.5
13	J. H.	39.8	29.7	199.0	11.00	57.4	46.4	30.2	25.0	5.2	26.7	3.5	3.3
14	A. F.	34.5	25.8	172.5	12.75	57.8	45.05	30.4	24.0	6.4	26.1	4.3	2.5
15	J. O.	33.4	25.0	167.0	13.15	80.0	66.85	45.7	35.0	10.7	38.6	7.1	3.2
16	V. H.	20.0	14.9	100.0	22.00	89.0	67.0	60.0	35.0	25.0	43.3	16.7	0
17	D. F.	24.3	18.2	121.5	18.10	80.1	62.0	45.7	32.3	13.4	36.8	8.9	1.4
18	J. F. *f*	31.5	23.7	157.5	13.95	66.0	52.05	34.5	27.3	7.2	29.7	4.8	2.3
19	J. F. *m*	26.7	19.9	133.5	16.50	78.6	62.1	43.6	32.3	11.3	36.1	7.5	1.9
20	E. R.	29.1	21.8	145.5	15.10	84.5	69.4	51.5	36.4	15.1	41.4	10.1	2.5
21	B. H.	23.3	17.4	116.5	18.90	73.4	54.5	39.1	28.5	10.6	32.0	7.1	0.9
22	D. B.	30.4	22.7	152.0	14.50	58.6	44.1	30.5	23.8	6.7	26.0	4.5	2.2
23	V. B.	28.2	21.1	141.0	15.60	75.0	59.4	41.3	31.0	10.3	34.4	6.9	2.0
24	R. W.	33.0	24.9	165.0	13.35	81.0	67.65	46.5	35.5	11.0	39.2	7.3	3.0
25	R. F.	34.0	25.5	170.0	12.95	70.9	57.95	37.3	30.2	7.1	32.6	4.7	2.8
26	J. M. *f*	24.7	18.3	123.5	17.80	78.0	60.2	42.5	31.5	11.0	35.2	7.3	1.6
27	A. S.	24.1	18.2	120.5	18.25	74.8	56.55	41.3	29.5	11.8	33.4	7.9	1.0
28	A. OC.	30.4	22.7	152.0	14.50	64.5	50.0	33.5	26.5	7.0	28.8	4.7	2.2
29	S. C.	25.5	19.1	127.5	17.30	91.0	73.7	66.0	39.4	26.6	48.3	17.7	2.3
30	E. L.	27.7	20.8	138.5	15.90	82.5	66.6	48.5	34.6	13.9	39.2	9.3	2.0

age gain amounting to 2.35 mm. Hg (Table III). It is of importance, however, to bear in mind that the gain from this factor depends to a

large extent on that derived from the dissociation curve. Table III shows that gradient III derived for hemoglobin alone averages 10 mm.

TABLE IV

Effect due to Flow

NO.	NAME	OBS. MIXED VENOUS O_2 CONTENT	O_2 CAPACITY	% SAT. MIXED VENOUS BLOOD	OBS. ART. PO_2	OBS. MIXED VENOUS PO_2	A–V ΔPO_2	MEAN CAP. PO_2	OBS. GRADIENT III	GAIN	SYSTEMIC FLOW L/MIN./M^2
1	V. S.	18.8	34.0	55.2	32.0	29.2	2.8	30.1	1.9	2.3	3.87
2	D. M.	18.2	28.5	64.0	45.0	33.2	12.8	37.5	8.5	−0.8	2.55
3	D. S.	17.6	32.0	55.0	33.3	28.8	4.5	30.3	3.0	1.5	3.70
4	O. J.	20.4	32.0	63.8	40.5	33.0	7.5	35.5	5.0	0.7	2.52
5	M. C.	22.8	35.3	64.5	36.0	33.5	2.5	34.3	1.7	3.0	8.40
6	L. S.	22.3	34.1	65.4	38.0	34.0	4.0	35.3	2.7	2.5	4.80
7	C. H.	14.6	26.3	55.5	31.8	29.2	2.6	30.1	1.7	3.5	5.89
8	R. A.	23.1	35.2	65.6	47.8	34.2	13.6	38.7	9.1	−1.6	1.84
9	J. S.	16.9	31.5	53.7	42.5	28.0	14.5	32.8	9.7	−3.5	0.90
10	R. C.	18.3	31.7	57.8	38.3	30.4	7.9	33.0	5.3	0	2.64
11	A. P.	13.7	21.0	65.2	53.0	34.0	19.0	40.3	12.7	−5.0	2.24
12	L. P.	19.8	30.3	65.4	44.0	34.1	9.9	37.4	6.6	0.4	2.38
13	J. H.	20.1	39.8	50.8	30.2	26.8	3.4	27.9	2.3	1.2	4.20
14	A. F.	17.5	34.5	50.8	30.4	26.8	3.6	28.0	2.4	1.9	8.20
15	J. O.	22.9	33.4	68.5	45.7	36.0	9.7	39.2	6.5	0.6	2.97
16	V. H.	9.6	20.0	48.1	60.0	25.6	34.4	37.1	22.9	−6.2	1.90
17	D. F.	16.5	24.3	67.9	45.7	35.4	10.3	38.8	6.9	2.0	3.90
18	J. F. *f*	16.3	31.5	51.8	34.5	27.2	7.3	29.6	4.9	−0.1	1.75
19	J. F. *m*	12.5	26.7	46.7	43.6	25.0	18.6	31.2	12.4	−4.9	1.50
20	E. R.	18.1	29.1	62.0	51.5	32.2	19.3	38.6	12.9	−2.8	1.23
21	B. H.	14.8	23.3	63.4	39.1	33.0	6.1	35.0	4.1	3.0	5.16
22	D. B.	12.1	30.4	39.5	30.5	22.0	8.5	24.8	5.7	−0.8	2.10
23	V. B.	15.2	28.2	54.0	41.3	28.3	13.0	32.6	8.7	−1.8	7.25
24	R. W.	20.5	33.0	62.3	46.5	32.6	13.9	37.2	9.3	−2.0	2.06
25	R. F.	19.3	34.0	56.8	37.3	29.8	7.5	32.3	5.0	−0.3	3.24
26	J. M. *f*	18.3	24.7	74.0	42.5	40.0	2.5	40.8	1.7	5.6	11.40
27	A. S.	13.7	24.1	56.8	41.3	29.4	11.9	33.3	8.0	−0.1	2.18
28	A. OC.	17.0	30.4	56.0	33.5	29.3	4.2	30.7	2.8	1.9	3.30
29	S. C.	17.1	25.5	67.1	66.0	35.1	30.9	45.4	20.6	−2.9	1.50
30	E. L.	19.1	27.7	69.0	48.5	36.2	12.3	40.3	8.2	1.1	4.20

which represents a considerable gain of 23 mm. over the gradient III of the normal individual at sea level. Since, however, the effect of the curve has already markedly reduced gradient III, the additional diminution in the gradient caused by the polycythemia is relatively small.

Similar considerations pertain to the evaluation of the effect of the systemic flow on gradient III. If the systemic flow is increased above

TABLE V

NAME	ART. PO_2 MM.Hg	MEAN CAP. PO_2 MM.Hg	TOTAL GRADIENT III PO_2 MM.Hg	GAIN IN GRADIENT III		
				Curve mm.Hg	Hgb mm.Hg	Flow mm.Hg
V. S.	32.0	30.1	1.9	26.0	2.8	2.3
D. M.	45.0	37.5	8.5	23.0	2.3	−0.8
R. S.	33.3	30.3	3.0	26.1	2.4	1.5
O. J.	40.5	35.5	5.0	24.7	2.6	0.8
M. C.	36.0	34.3	1.7	25.7	2.6	3.0
L. S.	38.0	35.3	2.7	25.1	2.7	2.5
C. H.	31.8	30.1	1.7	26.3	1.5	3.5
R. A.	47.8	38.7	9.1	21.9	3.6	−1.6
J. S.	42.5	32.8	9.7	24.4	2.4	−3.5
R. C.	38.3	33.0	5.3	25.1	2.6	0.
A. P.	53.0	40.3	12.7	19.7	5.6	−5.0
L. P.	44.0	37.4	6.6	23.5	2.5	0.4
J. H.	30.2	27.9	2.3	26.2	3.3	1.2
A. F.	30.4	28.4	2.4	26.2	2.5	1.9
J. O.	45.7	39.2	6.5	22.7	3.2	0.6
V. H.	60.0	37.1	22.9	16.3	0.	−6.2
D. F.	45.7	38.8	6.9	22.7	1.4	2.0
J. F. *f*	34.5	29.6	4.9	25.9	2.3	−0.1
J. F. *m*	43.6	31.2	12.4	23.6	1.9	−4.9
E. R.	51.5	38.6	12.9	20.4	2.5	−2.8
B. H.	39.1	35.0	4.1	25.0	0.9	3.0
D. B.	30.5	24.8	5.7	26.3	2.2	−0.8
V. B.	41.3	32.6	8.7	24.1	2.0	−1.8
R. W.	46.5	37.2	9.3	22.7	3.0	−2.0
R. F.	37.3	32.3	5.0	25.5	2.8	−0.3
J. M. *f*	42.5	40.8	1.7	24.1	1.6	5.6
A. S.	41.3	33.7	8.0	24.1	1.0	−0.1
A. OC.	33.5	30.7	2.8	26.1	2.2	1.9
S. C.	66.0	45.4	20.6	13.0	2.3	−2.9
E. L.	48.5	40.3	8.2	21.7	2.0	1.1
Arith. Mean....	41.6	34.62	7.12	23.6	2.35	0

normal, a significant gain from this factor may be expected in patients in whom the combined gain from the dissociation curve and the polycythemia is small. Conversely, a loss from this factor may result in patients with small systemic flows in whom the combined gain from the

dissociation curve and the polycythemia is large. The effect of this factor is further limited, since the systemic flow in tetralogy of Fallot is controlled by mechanical factors associated with the cardiac malformation (3). Table IV shows that 15 out of 30 patients show a slight gain, the rest some loss, in gradient. The average effect of this factor is zero.

The gains in gradient III are summarized in Table V.

SUMMARY AND CONCLUSIONS

The adaptive processes to anoxia in patients with congenital heart disease have been investigated. They have been discussed with reference to adaptations of normal individuals at high altitude. In the patients of this series the anoxemia was the result of the intracardiac shunt which increases the gradient of oxygen tension between alveolar air and arterial blood. On the other hand, in normal individuals exposed to high altitude, anoxemia is the result of decreased oxygen pressure in the inspired air.

At reduced barometric pressures, hyperventilation effectively lowers the total gradient of pO_2 between inspired air and mean capillary blood. In the patients of this series the presence of the intracardiac shunt nullified the effect of hyperventilation.

Another major difference was the low oxygen consumption observed in patients with congenital heart disease. The cause of the decrease in the basal metabolic rate is still obscure; it is possible, however, that it is the result of metabolic adjustments to prolonged severe anoxemia. In several patients with tetralogy of Fallot the oxygen consumption rose following the Blalock operation, indicating that the reduction of the metabolic rate may be reversible (21).

The adjustment of the acid base balance to anoxemia may be more effective in the patients of this series than in normal individuals at high altitude. In both cases hyperventilation results in a reduction of the partial pressure of carbon dioxide in plasma. At reduced barometric pressure the carbon dioxide deficit is not entirely compensated by a decrease in bicarbonate, and as a result the pH is elevated. In congenital heart disease with cyanosis, on the other hand, the bicarbonate content of plasma was reduced by an equivalent amount and the pH was maintained at normal values.

The pO_2 gradient from arterial to capillary blood (gradient III) is reduced in the patients of this series and in individuals exposed to high altitude. In both conditions this reduction is mainly the result of the shape of the oxygen dissociation curve and to a lesser extent of an increase in the oxygen carrying capacity of the blood. The systemic flow shows an initial increase in normal individuals exposed to lowered barometric pressure and thereby lowers gradient III.

Despite individual variations in the patients of this series, the average effect of their systemic flows did not alter the gradient.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Care and Management of Laboratory Animals, The. Edited by ALASTAIR N. WORDEN. Illus. 368 pp. $8.50. *The Williams & Wilkins Company, Baltimore,* 1947.

This handbook of the Universities Federation for Animal Welfare is an excellent British text which is full of both the everyday useful information, such as how to pick up and hold a rabbit or how to house and feed different species of rats, and more obscure (to us) information such as anaesthesia of hedgehogs. Besides the rabbit, guinea pig, several kinds of rats and mice, there are chapters on voles, hamsters, ferrets, pigeons, canaries, amphibia and freshwater fish, each obviously by an individual who is actively working with the animal in question. A separate chapter on Law and Practice or The Rights of Laboratory Animals is particularly interesting to workers in this country. Herein is indicated the much stronger hold the anti-vivisectionists have on the use of laboratory animals in England than here. Laws and regulations, at least on paper, completely control the use of animals in research. Different classes of animals are established and different classes of investigation are permissible. In a way this chapter is a renewed warning to laboratory workers that the public has a right to insist on the most humane type of care of animals and that we must recognize that right.

It is impossible for one person to review adequately such diversified although concisely arranged information, but the reader may note that, although the publication date is 1947, there is little new information on the use of insecticides in the chapter on "Pests of the Animal House and their Control" by Buxton and Busvine, apparently because this chapter was written in 1944. Thus there is nothing on Gammexane against cockroaches.

There are no chapters on anthropoids, dogs, cats, or poultry, but there are a few scattered notes in the last chapter giving good references.

A conspectus of the Elements of Statistical Analysis is included in this book with the thought that the appreciation of the value of a statistical approach will help the reader to use fewer animals in his experiments. No doubt this is a useful chapter but still seems out of place in a practical handbook.

There is no question but that the excellence of this much needed handbook will make it necessary in all laboratories where small animals are used.

F. B. B.

Identification of Tumors. By NATHAN CHANDLER FOOT. Illus. 397 pp. $6.00. *J. B. Lippincott Co., Philadelphia.* 1948.

The author's preface anticipates the reviewers' comments regarding the discrepancy between the comprehensive implication of the word "identification"

and the brief discussion of human tumors as presented. The book is offered as a "ready reference" book on human tumors. It is short, "systematically compiled", and affords "an adequate concept of the salient gross and microscopic features and the means for diagnosis of the various tumors". The book is written with definite objectives: To "refresh" the knowledge of physician and surgeons and enable them "to glean the essentials without having to sift them out of a mass of historical and theoretical data, academic discussion, clinical discussion and other such material that is regularly found in the few books that deal with the subject of new growths". The author ends the preface by the sentence: "This will necessitate a personal, arbitrary and didactic approach which, it is hoped, will be understood and condoned by the reader".

An aggressive attempt has been made to realize the ambitious objectives, which are developed to a degree sufficient to warrant recommendation of the book for the uses indicated by the author.

W. B. V.

Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, A. 7th edition. By TORALD SOLLMANN. 1132 pp. $11.50. *W. B. Saunders Company, Philadelphia, Pennsylvania*, 1948.

The seventh edition of Sollmann's "A Manual of Pharmacology" brings a thorough revision of this important text. The far reaching developments of the past decade have called into being new sections on such topics as antibiotic substances, antithyroid drugs, antimalarials, the sulfonamide compounds, and the antihistamine agents. This volume represents a most exhaustive and detailed compilation of the multitudinous details of drug action, well organized, brought up-to-date, presented with discrimination and well documented with references to the original literature. Sollmann's *Manual* represents the most comprehensive reference volume to have at hand when confronted with a specific problem regarding the action of a drug.

M. R.

Modern Clinical Psychiatry. 3rd edition. By ARTHUR P. NOYES. 525 pp. $6.00. *W. B. Saunders Company, Philadelphia, Pennsylvania*, 1948.

This latest edition of Dr. Noyes' widely read textbook contains three new chapters on psychotherapy, shock and other physical therapies and child psychiatry. In discussing psychotherapeutic methods the author stresses the psychobiological approach and presents a rather clear account of what is meant by it. Psychoanalytic methods are adequately described and should acquaint the reader not only with their aims but also with some technical aspects of procedure. Shock therapies are discussed in some detail; however, the author seems fully aware of their limitations, pointing out the importance of adequate psychotherapy being available for patients receiving such treatment. The most useful feature of this book is its dynamic orientation and the author's ability to present dynamic psychiatry in a style which can be easily understood by the student. The experienced psychiatrist

will find it stimulating reading and should be able to make ready use of the very excellent bibliography at the end of each chapter.

E. A.

Noah Webster: Letters on Yellow Fever Addressed to Dr. William Currie. 110 pp. $2.00. *The Johns Hopkins Press, Baltimore, Maryland,* 1947.

Eighteenth century America was peculiarly fortunate in its possession of many men whose breadth of interests perplexes the twentieth century specialist. Noah Webster was typical of his time. Not only was he a lexicographer and the author of the American Spelling Book, which ran to 60,000,000 copies, but he was, variously, a lawyer, newspaper editor, statistician, climatologist, economist, and epidemiologist. This small volume of *Letters on Yellow Fever* summarizes some of Webster's epidemiologic views. A contagious disease, he wrote, is one which is communicated from person to person either by contact or near approach. It must be distinguished from infectious disease, which requires for its propagation crowding, hot weather, close rooms, and so forth, all of which generate an epidemic constitution to the atmosphere. Yellow fever belongs to this latter group of diseases. It is useless to quarantine ships from the Indies, since yellow fever is not imported but arises locally as the result of an epidemic constitution to the atmosphere. Moreover, wrote this Federalist, the view that yellow fever is imported is dangerous to our growing commerce. The proper protection against yellow fever is careful planning of our cities to combine the best features of country and city.

These interesting letters are preceded by an entertaining introduction by Benjamin Spector.

O. D. R.

Practical Clinical Psychiatry. By Edward A. Strecker, Franklin G. Ebaugh and Jack R. Ewalt. 6th Edition. Illus. 476 pp. $5.00. *The Blakiston Company, Philadelphia, Pennsylvania,* 1947.

Although the 6th edition of this popular text has several new chapters, such as those on pathologic drinking and psychosomatic medicine, the general orientation of its contents is essentially unaltered. Written primarily for the medical student and following psychobiological principles, it should prove useful to the beginner to become acquainted with fundamental aspects of psychiatric examination, classification, and, to a lesser degree, with those of psychiatric treatment.

The book's greatest asset is its good organization, and its chief liability is a relative lack of dynamic orientation, particularly as regards the psychoses. The chapter on "Psychosomatic Medicine" is very likely to confuse the reader, being ill-defined and creating the impression that physiological expressions of anxiety as such constitute "psychosomatic" disease.

The chapter on toxic psychosis is very complete and well presented. The problem of alcoholism receives considerable attention in this chapter and also in a separate section on "Pathologic Drinking."

Dr. Kanner's discussion of childhood problems is essentially identical with the corresponding chapter of the preceding editions.

In addition to its value to the medical student, the text is likely to serve as a ready reference for the busy practitioner who, as a result of its uncomplicated presentation of clinical psychiatry, should have little difficulty in grasping its contents. E. A.

Signs and Symptoms: Their Clinical Interpretation. Edited by CYRIL MITCHELL MACBRYDE. Twenty Contributors. Illustrated. 439 pages. $12.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1947.

This is a valuable book for practitioners, medical students and specialists alike. The subject matter is dealt with in monographic form. Twenty contributors of eminence have written upon pain, headache, sore tongue and sore mouth, thoracic pain, abdominal pain, backache and back pain, joint pain, pain in the extremities, fever, disturbances of consciousness and muscle movement, fainting, dyspnoea, cyanosis, dehydration, edema, palpitation and tachycardia, cough, hemoptysis, obesity, weight loss and undernutrition, anorexia, nausea and vomiting, constipation and diarrhoea, hematemesis and melena, jaundice, itching, nervousness and fatigue.

The authors approach diagnosis from an analysis of the account the patient gives of his symptoms and the signs the examiner finds. There are sound discussions of the fundamental pathologic physiology responsible for signs and symptoms. The discussions indicate clearly the lines of special study by clinical and laboratory techniques which will be likely to enable the investigator to arrive at precise diagnoses.

The book is well illustrated both in black and white and in color. There are numerous charts and tables, and the bibliographies, for the most part, are well chosen and complete.

The chapter on headache by Harold G. Wolff is unusually well done. The mechanisms responsible for headaches of all sorts are described. Various factors which enter into the production of clinical pictures of which headache is the chief feature are discussed thoroughly. Anyone not entirely familiar with the problems of head pain will have a very clear concept of the subject after reading this chapter.

The book is enthusiastically recommended. B.M. B.

Submicroscopic Morphology of Protoplasm and its Derivatives. By A. FREY-WYSSLING. Illus. 255 pp. $6.00. *Elsevier Publishing Company, Inc., New York, New York,* 1948.

This first English edition is really a second edition of "Submikroskopische Morphologie des Protoplasmas und seiner Derivate", published in 1938. At that time it was something of a classic summary of the indirect experimental data indicating a definite ordered structure to material below the microscopic level of vision. Since then a great deal more data, such as that furnished by x-ray patterns, anisotropy of swelling, and polarization microscope techniques have been applied to the study of fine structure. A good summary of this is presented. Data yielded by

the direct method of electron microscopy are presented briefly in the text. It is pointed out that this method cannot be the sole means of asking pertinent questions. New facts or artifacts seen by the electron microscope must be evaluated in relation to all of the other indirect data.

It is too bad, in the light of this, that the few pictures presenting the case for study of submicroscopic structure by electron microscopy are so poor. Perhaps this reflects the lack of availability of such data to European authors during the war, and it is to be expected that this will be corrected in a future edition of this very worthwhile text.

F. B. B.

Textbook of Surgery for Nurses. By EDWARD S. STAFFORD AND DORIS DILLER. Illus. 577 pp. $3.25. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1947.

This is an excellent text. The style is simple and informal and the subject matter a tribute to the dignity of the nursing profession. The approach is based on the conviction that a nurse will give better care to patients if she understands the general pathology of a disease and the aims and technics of the surgeon in treating them. Each important condition is therefore introduced with appropriate background material, and then the matters pertaining more strictly to ward nursing are brought in and their rational basis made clear. Two-thirds of the book is on surgery. The remaining portion is devoted to the special fields of surgery: neurosurgery, ophthalmology, otolaryngology, genito-urinary, and gynecological surgery. There is an abundance of common sense throughout the book based on the wide experience of the two authors. Although much of the material is written so straightforwardly that it would be interesting reading for a layman, the book could be recommended strongly to third and fourth year medical students who are about to begin their ward apprenticeships. It is expected to have a wide field of usefulness in the training of nurses. The illustrations are numerous and are diagrammatic in type.

W. E. G.

Treatment in General Practice. 6th edition. By HARRY BECKMAN. 1129 pp. $11.50. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1948.

This new edition of an old favorite textbook lives up in every way to the high standards of the previous editions. The general pattern of preceding volumes is closely followed, but a large amount of revision shows in almost every topic. Recent advances are well covered. The bibliography is large and well chosen, as well as up to the minute. The style is as engaging as ever, written in a personal way, amusing and even a trifle saucy, but always quickly moving and rarely bogging down in argument or disagreements. The reader may not agree with every detail, but the over-all picture is clear and well presented. This edition is highly recommended as a textbook or reference source.

J. A. L., Jr.

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Clinical Laboratory Methods and Diagnosis. 4th edition, 3 vols. By R. B. H. GRADWOHL. Illus. 3148 pp. $40.00. *The C. V. Mosby Company, St. Louis, Missouri,* 1948.

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